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Respiratory Diseases

Fernand Widal Syndrome: About 16 Cases (Moroccan Series)

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Abstract **Original Research Article**

Fernand Widal syndrome is a condition with an often severe triad of asthma, intolerance to acetylsalicylic acid and nasosinus polyposis. Aim of the work: to determine the clinical peculiarities of the patients carrying this syndrome in our context.Patients and methods: we carried out a retrospective study carried out over a period of five years at the service of respiratory diseases of the University Hospital of Casablanca, collecting 16 cases of patients carrying this triad. Result: The average age was 44.2 years, with a female predominance (75% of cases). All patients had atopy, mainly rhinitis and conjunctivitis. In 62.5% of the cases, asthma was moderate to severe with moderate to severe obstructive airways in 60% of cases. Five patients had a history of hospitalization for severe exacerbation of asthma in one medical facility and four others in intensive care unit with intubation in three patients. All patients were on inhaled corticosteroids and long-acting bronchodilators using antileukotrienes. Despite optimal medical treatment and polyp surgery in patients with locally resistant rhinitis, 38% of rhinitis cases and 56.6% of severe asthma cases were poorly controlled. In conclusion, patients with SFW have difficult-to-control asthma and rhinitis under optimal medical treatment, sometimes requiring desensitization with aspirin and the emergence of new therapies.

Keywords: Nasal polyposis; rhinitis; asthma; Fernand Widal syndrome; aspirin sensitivity.

INTRODUCTION

Fernand Widal syndrome (FWS) comprises a clinical triad of asthma, chronic rhinosinusitis with nasal polyposis, and intolerance to acetylsalicylic acid (Aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs). It is estimated that 7% of asthmatics and 10% of patients with chronic rhinosinusitis suffer from it. Asthma and NSAID hypersensitivity usually appear several years after the onset of rhinosinusitis, delaying diagnosis. Asthma in SFW is associated in the literature with corticosteroid resistance and is often poorly controlled. Our objective is to study the clinical, therapeutic and evolutionary characteristics of our patients with this triad.

PATIENTS AND METHODS

We conducted a retrospective study carried out over a period of five years, at the respiratory diseases department of the university hospital of Casablanca. We collected 16 cases of patients with the triad made of asthma, nasosinusal polyposis and intolerance to aspirin or other NSAIDs. Medical records were reviewed and clinical information was collected on a pre-established form. Signs of intolerance to aspirin were sought by questioning, by the appearance or aggravation of respiratory discomfort when taking these drugs. The data collected were analyzed using the professional statistical analysis software SPSS 1.0.1(version 2017).

RESULTS

We collated 16 patients with SFW followed up in an allergology consultation over a 5-year period (2014-2018). The average âge was 44.2 years with extremes ranging from 17 to 66 years.

We noted a female predominance in 75% of cases with a M/F sex ratio of 0.3. The average age of onset of asthma was 25 years.

Family atopy was found in 68.7% of cases. Personal atopy was found in all our patients, such as allergic conjunctivitis (62.5%), food allergy (37.5%), eczema (31%) and atopic dermatitis (31%). Drug allergy to penicillin was found in 18.7% of patients.

Allergic rhinitis was present in all our patients; made of nasal obstruction in 11 cases, nasal discharge in eight cases, sneezing in four cases, anosmia in one

patient and nasal pruritus in five cases. Rhinological signs evolved before the diagnosis of asthma in three patients. Rhinitis was intermittent in three cases, persistent in 13 patients; classified as mild in four patients and moderate to severe in nine patients.

Six patients had a history of hospitalization for asthma exacerbation in a medical department and four others in the intensive care unit, with intubation in three patients. A history of long-term oral corticosteroid therapy was found in seven patients and frequent recourse to the emergency room in ten patients. Other comorbidities were arterial hypertension in five cases, adrenal insufficiency in three patients, diabetes in two patients and one case each of thyroid cancer and obstructive sleep apnea syndrome.

Apart from aspirin use, other triggers for clinical symptoms were identified (Figure I). These clinical symptoms were present perennial in six patients and during the winter and spring period in the other patients.

Asthma was initially classified as intermittent in one case, moderate to severe persistent in ten patients and mild in the others. An onset or worsening of respiratory symptoms when taking aspirin was present in all our patients, with anaphylactic shock noted in one patient and facial edema in three others. Spirometry was performed in 15 patients and concluded to an obstructive ventilatory disorder in nine patients, classified as moderate to severe (Figure II). It was normal in six cases. The prick test performed in four patients was in favor of a polysensitization in all cases. In addition to the avoidance of aspirin and NSAIDs, which remains essential, the medical treatment of asthma was based on medium- to high-dose inhaled corticosteroids associated with long-acting bronchodilators in 75% of cases, and inhaled corticosteroids alone in 25% of cases.

The treatment of rhinosinusitis was based on nasal corticosteroid therapy in all our patients associated with antihistamines in 50% of cases. Antileukotrienes were prescribed in two patients (12.5%). Polypectomy was performed in four patients, after which only two patients had an improvement of rhinitis and asthma symptoms.

Despite optimized treatment, asthma was uncontrolled in nine (56.5%) patients. We had one death in the ICU for severe acute asthma. Improvement of rhinitis signs under medical treatment alone was noted in ten cases (62.5%).

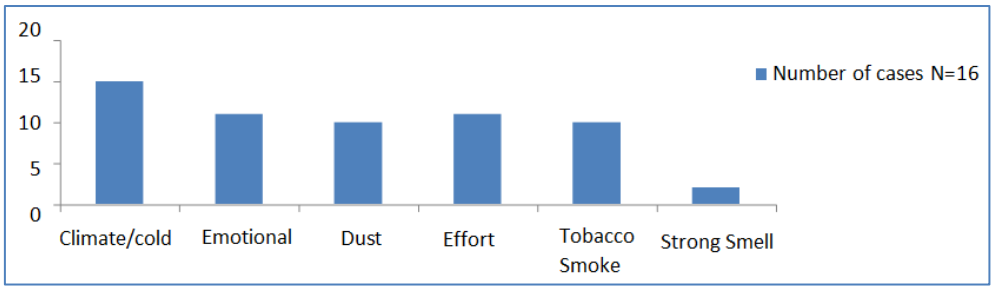

Fig-I: Triggering factors of asthma and rhinitis

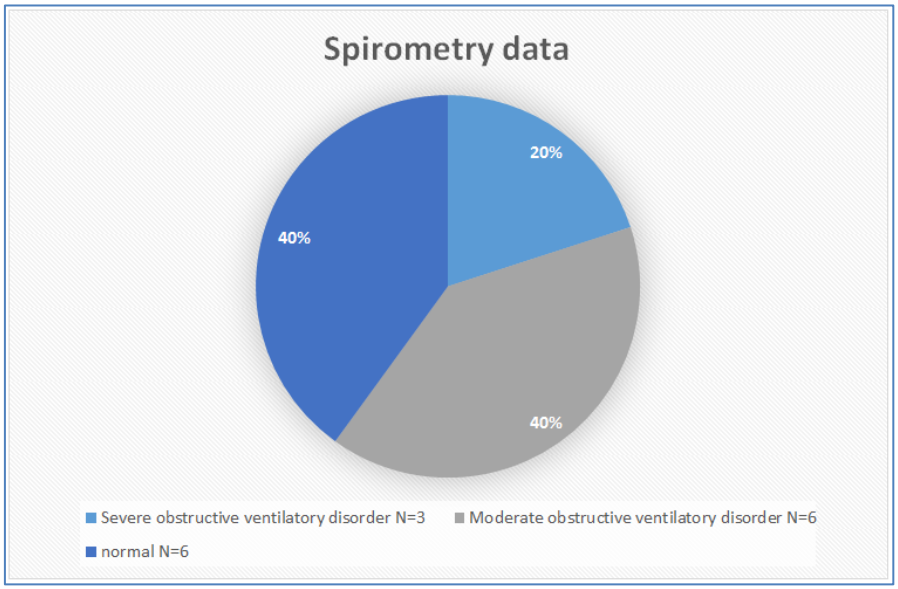

Fig-II: Spirometry data

DISCUSSION

Discovered in 1897 by Hoffmann, aspirin is one of the most widely used drugs in the world. In 1929, F. Widal et al. published the first case of aspirin intolerance with a respiratory form combining asthma, nasosinus polyposis and intolerance to acetylsalicylic acid [1, 3].

In 1975, the concept of intolerance to aspirin was extended to all NSAIDs, allowing the allergic hypothesis to be rejected and giving way to biochemical explanations by an imbalance in the metabolism of arachidonic acid, which leads to an increase in the infiltration of eosinophils and activated mast cells in the respiratory mucous membranes, outside of any aspirin intake. Activated epithelial cells and Th2 lymphocytes synthesize greater quantities of pro-inflammatory cytokines and excessive quantities of leukotrienes. The synthesis of these leukotrienes is amplified by aspirin and NSAIDs through inhibition of the cyclooxygenase pathway of arachidonic acid degradation [3-5].

The prevalence of SFW or Triad Samter in English speakers is 7.15% according to a meta-analysis of studies conducted in asthmatic patients [2]. In another recent study in the USA, the prevalence of SFW was 3-20% in asthma patients [6]. It typically occurs in adults between 30 and 40 years of age, with a predominance of women who carry the most severe forms [3, 6].

In our study, its prevalence was 4% with a female predominance. Our average age is 44.25 years. In a review published in 2018[7], atopy was present in 2/3 of the patients while there was most often no associated atopic terrain in other literature [1]. A lack of familial form of SFW has been noted [6]. No similar cases in the family were found in our patients but familial atopy was present in 68% of our patients.

The diagnosis is usually based on the interrogation in the complete forms. The presence of aspirin intolerant asthma should strongly suggest the diagnosis. However, the clinical picture may be incomplete at first, with isolated ENT signs [4-6]. Nasosinus polyposis (NSP) is a particular form of chronic sinusitis, characterized by the bilateral and multifocal development of polyps, the diagnosis of which is based on nasofibroscopy and imaging showing a more or less marked tissue filling of the nasosinus cavities. Asthma most often occurs 2 to 3 years after the signs of rhinitis and usually precedes nasal polyposis in 2/3 of cases [3, 6]. In our series, ENT signs preceded asthma in three patients.

Intolerance to NSAIDs, including aspirin, leads to respiratory gênes due to more or less severe bronchospasm. Other symptoms may be associated notably ENT and ocular: sneezing, nasal pruritus, lacrimation and ocular erythema, even moderate periorbital edema.

Some patients report the occurrence of an erythematous rash of the face and neck. The intensity of the symptoms varies from simple rhinitis to life-threatening anaphylactoid manifestations. In our series, the use of aspirin induced the appearance or aggravation of dyspnea in all our patients. Facial edema was noted in three patients and anaphylactic shock in one patient [3].

The diagnosis of SFW is based on clinical data and on the oral challenge test, which consists of administering increasing amounts of aspirin every 20 minutes. A fall of at least 20% in FEV1 or the appearance of extrathoracic symptoms (rhinorrhea, erythema, and conjunctivitis) allows the test to be considered positive [5, 6]. It should be reserved for patients with stabilized asthma without a history of severe attacks following the use of NSAIDs, severe underlying pathology, recent respiratory infection, current pregnancy, or use of beta-blockers [3, 8]. The mechanism is not allergic; therefore, skin tests and the search for specific IgE are not appropriate [1, 3].

However, there are other provoking mechanisms in patients with SFW. These include exacerbations of asthma and rhinitis following viral infections, gastroesophageal reflux, and irritation, and exercise, exposure to pollen, dust, animals and food. These triggers were also found in our study [7].

According to several studies, SFW is associated with more severe signs of rhinitis and asthma with frequent exacerbations [7, 8].

Our patients had moderate to severe rhinitis in 56% of cases and moderate to severe asthma in 62% of cases. The particularly obstructive nature of nasal polyposis, often associated with anosmia, altered the quality of life of the patients. Nasal obstruction was present in 11 patients, only one of whom had anosmia.

The management of this syndrome remains difficult given the frequency of exacerbations and recurrence of même polyps with optimal medical treatment. Avoidance of cyclooxygenase cycle inhibitors notably aspirin and other NSAIDs is advocated upon suspicion of SFW.

Corticosteroids and antileukotrienes are the first therapeutic treatments used. Inhaled and systemic corticosteroids relieve subjective and objective symptoms. Intranasal corticosteroids such as fluticasone propionate have been shown to decrease the number of inflammatory cells, including eosinophils and mast cells [6]. A multicenter randomized trial showed that leukotriene antagonists such as montelukast improved lung function and asthma control compared to

conventional corticosteroids alone and were an attractive combination therapy [6, 9]. However, as medical treatment remains insufficient to control symptoms, aspirin desensitization may provide additional benefits.

Although avoiding surgery is one of the main goals of medical treatment [7,8], surgical reduction of nasal polyps and endoscopic nasal polyps and functional endoscopic sinus surgery provides sinus ventilation and facilitates the delivery of topical medications and the removal of an inflammatory nidus (eosinophilic polyps).

Surgery improves signs of rhinitis and asthma [1, 6]. Aspirin intolerance seems to be associated with a higher recurrence rate after surgery for nasosinusal polyposis. However, a multidisciplinary management between ENT and pulmonologist with recourse to desensitization, when possible, would improve the symptomatology and decrease the number of repeat surgeries from once every three years to once every 10 years [6,7,11]. Aspirin desensitization is recommended shortly after sinus surgery, i.e., three to four weeks after the first surgery. However, the duration of the surgery requires further research [6-8, 11].

The emergence of biotherapies, such as omalizumab, has led to a reduction in the size of polyps with a decrease in respiratory symptoms and the use of hospitalizations with lower leukotriene levels in urine samples [6]. Mepolizumab, reslizumab, benralizumab and dupilumab are other molecules that have been shown to have a satisfactory effect on nasal polyps in patients with SFW [6, 10].

CONCLUSION

SFW remains an entity whose frequency is underestimated. Our study found a syndrome that causes severe asthma and rhinitis, difficult to control with optimized medical treatment, which is in line with the data in the literature. An early diagnosis avoids inappropriate prescriptions and collaboration between ENT and pneumologist remains necessary for the management of this disease.

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