Prevalence of comorbidities in multiple sclerosis patients with neurogenic bladder

Aims. — The aim of this study was to define the prevalence of comorbidities among multiple sclerosis patients with lower urinary tract symptoms.

Methods. — A retrospective study of data collected prospectively from January 2000 to March 2016 was carried out using a database. Comorbidities were divided into several classes according to the International Classification of Diseases (ICD-10).

Results. — One hundred and fifty-five patients were included. All had a neurogenic bladder with 150 (96%) overactive bladder. EDSS score was ≥ 6 in 44 patients (28%). Comorbidities were present in 79 (50,9%) and the most frequent ones were cardiovascular (14,2%), endocrinological (10,3%), urological (8,4%), abdominal (7,7%). Overweight (BMI ≥ 25) was observed in 63 (40%). A strict relationship was found for BMI and stress urinary incontinence (p < 0.001) as well as voiding dysfunction (P = 0.003) without significant association for BMI and overactive bladder.

Conclusion. — Prevalence of comorbidities is important in MS (more than 50%). A significant association is found between overweight, stress urinary incontinence and voiding.
Introduction

Urinary disorders are often observed in multiple sclerosis (MS) patients and appear six years after the onset of neurological symptoms [1]. These symptoms affect nearly 90% of patients with MS [2], lead to urological complications and seriously impact quality of life. Overactive bladder (OAB), combined with urgency, frequency, nocturia and urge incontinence, is the most common syndrome, which is sometimes associated with voiding dysfunction and urinary retention. The most common urodynamic pattern is the association of overactive detrusor with detrusor-sphincter dyssynergia. Complications of the lower and upper urinary tract are less frequent than those observed in spinal cord injury patients but nevertheless reported in 12% of cases: upper and lower recurrent urinary tract infections, reflux, renal failure, upper urinary tract dilatation [2,3].

Usually, all these urinary symptoms are considered as a specific part of the neurological disease within the general concept of neurogenic bladder. Nevertheless, other etiologies (urological, gynecological, metabolic, iatrogenic...) [4] can be observed in MS. These states with non-disease-related health alterations are called "comorbidity". Comorbidity was defined by Feinstein as "any distinct clinical condition that coexists or may occur during the course of an index disease in a patient" [5].

Thus, six meta-analysis carried out in 2015, using data on the incidence and prevalence of comorbidities associated with MS from 249 studies conducted between 1905 and 2012, revealed that depression, anxiety, high blood pressure, hypercholesterolemia and chronic lung disease constitute the 5 principal prevalent comorbidities in MS with a high prevalence. In addition, studies show that these comorbidities are more common in men, of an older age [6–11]. Psychiatric comorbidities are common in MS [12]. Otherwise, it has recently been shown a significant association between several pathologies and overactive bladder, such as obesity, diabetes, metabolic syndrome or cardiovascular diseases [13,14]. Thus, as comorbidities are frequently observed in MS and as these comorbidities can modify urinary function, it can be questionable to verify the impact of these comorbidities on the urinary symptoms and urodynamic patterns in MS. However, to our knowledge, there are no studies evaluating these impacts on urinary disorders in patients with MS.

The aim of this study was to define the prevalence of comorbidities among multiple sclerosis patients with lower urinary tract symptoms according to disease severity and overweight. The secondary objective was to assess a possible relationship between one or more comorbidities including overweight and the severity of the lower urinary tract symptoms.
Methods

Design of the study

A retrospective study of data collected prospectively from January 2000 to March 2016 was carried out using a database of a university neuro-urology department. These data included reports of medical consultations and urodynamic studies.

Patients

All patients with MS diagnosed according to the revised criteria of McDonald’s (2005 and 2013) [15], aged 18 years and older, consulting for lower urinary disorders were identified and included. Patients were in the presence of indwelling catheter, noxious stimuli (infection, bedsores...) or any acute event.

Variables

In order to define, as the primary endpoint of the study, the prevalence of comorbidities in these patients, the data were collected from the medical reports (during the first patient visit a complete examination from his medical history was made). The different comorbidities were deduced from the last clinical report. These were divided into several classes according to the International Classification of Diseases (ICD-10): cardiovascular, endocrinological, digestive, immunological, oncological, neurological (other than MS), psychiatric, respiratory, orthopedic and rheumatological, gynecological, urological (i.e. urological conditions other than neurogenic bladder). The existence of diabetes has been reported separately; if comorbidity could not be classified, it was categorized as "other comorbidities".

For each patient, age, gender, severity of neurological disability measured by the Expanded Disability Status Scale (EDSS) [16], Body Mass Index (BMI), Urinary Symptoms Profile (USP) [17] score and urodynamic diagnosis (overactive or underactive detrusor) were reported from the data of the last consultation. The 3 USP sub-scores were obtained from these data: USP overactive bladder score (USP OAB), USP voiding dysfunction score (USP VD), and the stress urinary incontinence score (USP SUI). Urodynamic diagnosis was determined on the last urodynamic assessment by an experienced neuro-urolgist, as defined by International Continence Society [18]. Different symptoms were noted, such as the existence of an overactive bladder syndrome (with urgency, nothuria, increased daytime urinary frequency...), the presence of voiding symptoms (slow stream, hesitancy..., or a urinary retention (with a post voiding residual of 100 ml or more). The urodynamic traces from each study were manually inspected and artefacts corrected. An involuntary detrusor contraction was defined as a sudden rise in detrusor pressure of any magnitude, whether spontaneous or provoked without rise in abdominal pressure, if such contraction was observed the patient had a detrusor overactivity, if not the patient was classified as "no detrusor overactivity". During the urodynamic examination, the bladder sensation were asked to the patient. The urodynamic studies were performed according to "the Good Urodynamic Practice" recommended by the International Continence Society (ICS) [19]. All definitions used were in accordance with the International Continence Society Report [20].

Statistical analysis

All the statistical analysis were carried out using the analysis software R 3.2.3 software (R development Core Team, http://www.R-project.org) and R studio version 1.0.136. Descriptive statistics were used to identify the prevalence of comorbidities. The categorical variables were analyzed using a Chi-2 test or an exact Fisher test when the number of subjects was insufficient (n<5); The comparison of the means was made by means of a Student’s T test. A P<0.05 level was considered statistically significant.

A Spearman test was performed to find a correlation between the BMI and the USP score and the different USP subscores.

Ethics

This study was approved by the local ethics committee. Since it was a retrospective study, no formalized informed consent was necessary according to the ethics committee, and a letter was sent to the patients informing them that their data would be used, unless they contacted the investigators to express their disapproval.

Results

Démographic data (Table 1)

The demographic and clinical data of 155 patients with a diagnosis of MS were analyzed. Most of the patients were women (n=110, 71.1%). Patients were divided into two groups: those without comorbidities (n=76, 49.4%) and those with one or more comorbidities (n=79, 50.6%). Patients were also classified as having an EDSS greater than or equal to 6 (n=44, 28.0%) or less than 6 (n=111, 72.0%). They were also classified as being overweight, defined by a BMI greater than or equal to 25 kg/m² (n=93, 60.0%) or not (n=62, 40.0%). Among these patients, the most common symptomatology were overactive bladder syndrome (n=132, 84.6%), voiding symptoms (n=135, 87.0%). In our population, 102 patients (65.4%) had incontinence and 91 had urinary retention (58.3%).

Comorbidities prevalence

Among these 155 patients, the prevalence of comorbidities was 50.6%, categorized as follows: cardiovascular (n=22, 14.2%), endocrinological (n=16, 10.3%), urological (n=13; 8.4%) (i.e. urological conditions other than neurogenic bladder), abdominal (n=12, 7.7%), orthopedic and rheumatologic (n=12, 7.7%), neurological (n=9, 5.8%), diabetic (n=7, 4.5%), autoimmune (n=5, 3.2%), respiratory (n=4, 2.6%), gynaecological (n=4, 2.6%). Concerning the cardiovascular comorbidities, the most prevalent were: High blood pressure (n=15; 9.6%) and myocardial ischemia (n=3; 1.9%). Among the endocrinological comorbidities, the most common were: dyslipidemia (n=8; 5.1%) and thyroid dysfunction (n=6; 3.9%).
Comorbidities prevalence according to overweight (Table 2)

There were 63 patients (40.0%) in the overweight group (mean BMI of 28.3 ± 3.0 kg/m²), 40.6% were male, the mean age was 52.7 ± 11.7 years, and the mean EDSS was 5.0 ± 2.4. 60.9% of overweight patients had at least one comorbidity. Among the 92 (60.0%) non-overweight patients (mean BMI of 21.2 ± 2.3 kg/m²), 20.9% were male, the mean age was 49.3 ± 11.4 years, and the average EDSS score was 4.9 ± 1.7. 43.9% of these patients had at least one comorbidity. There was no association between BMI and the presence of comorbidity (P = 0.08), nor association between the presence of overweight and the type of comorbidity.

Comorbidities prevalence according to EDSS score (Table 3)

Among the 111 (72%) “ambulatory” patients (mean EDSS score 4.1 ± 1.5), 22.5% were male, mean BMI was 24.0 ± 4.5 kg/m², mean age was 49.3 ± 11.8 years. 56 (50.5%) of these patients had at least one comorbidity. Among the 44 patients (28.0%) with an EDSS score above 6 (mean EDSS score of 7 ± 0.4), 45.4% were male, mean BMI was 24.5 ± 4.0 kg/m², and mean age was 54.2 ± 10.3 years. Of these, 23 (52.3%) patients had at least one comorbidity. There was no association between the degree of neurological disability measured by the EDSS score and the presence (or the type) of comorbidity (P = 0.19).

Association between USP score and comorbidities prevalence (including overweight)

There was no association between the presence of comorbidity and a high USP score (P = 0.87) and for each different sub-scores except a positive association between BMI, the USP voiding dysfunction sub-score (rho = 0.25, P = 0.003) and the USP stress urinary incontinence score (rho = 0.277, P < 0.001). In contrary and surprisingly, we have not found any association between BMI and USP overactivity sub-score (rho = 0.14, P = 0.09).

Association between comorbidities prevalence and urodynamic characteristics

In this MS population, there were 112 patients with detrusor sphincter dyssynergia (71.8%), and 146 had bladder feeling during the evaluation. None of them had a compliance alteration. A hundred and fifty patients (96.1%) had overactive detrusor, which was controlled by specific treatments (anticholinergics, intra detrusor botulinum toxin injections) in 40.7% of the cases. There was no significant difference between the urodynamics characteristics and the existence or not of one or more comorbidities.

Discussion

This study assesses the prevalence of comorbidities in a cohort of MS patients with lower urinary tract dysfunction and the impact of these comorbidities on urinary symptoms and urodynamic patterns. The most common comorbidities...
were overweight, cardiovascular, endocrinological and urological. The distribution is slightly different in groups of patients with and without overweight as well as in patients with higher EDSS score although cardiovascular comorbidity remains the first one in term of frequency in these two groups. A significant association was found between overweight and the existence of stress urinary incontinence and voiding dysfunction. On the contrary, no association was found between comorbidity and overactive detrusor.

To our knowledge this is the first study evaluating the association of these comorbidities with lower urinary disorders in MS patients.

### Comorbidities and multiple sclerosis: review of literature

A study of a sample of 2399 MS patients recruited on social networks in 2016 showed that approximately two thirds of these patients had at least one comorbidity. Comorbidities with the highest prevalence were low back pain (36.2%), depression (31.7%), osteoarthritis (13.7%) and arterial hypertension (11.2%) [21]. A study by Marrie et al. showed that 48% (n=4264) of patients had psychiatric comorbidity. It was depression in 46% (4012 subjects), anxiety (16.5%, 1444 subjects) and bipolar disorder (2.4%, or 213 subjects) [10]. In the meta-analysis performed by Marrie et al. in 2015, the most frequent comorbidities were depression, high blood pressure, dyslipidemia, and chronic respiratory insufficiency [9]. The differences in prevalence with our study can be explained by the mode of data collection, an exclusive European population (without American and Asian patients) and a MS selected cohort with all the patients suffering from urinary disorders.

### Results: comorbidities prevalence

In all the groups in our study, cardiovascular comorbidities have the highest prevalence. They are particularly represented in the “overweight” subgroup, which is consistent with the known association between overweight and...
the existence of cardiovascular risk factors. Cardiovascular comorbidities are also well known to be responsible for direct urinary disorders due to a chronic pelvic ischemia [22], or secondary to an iatrogenic effect of many cardiovascular drugs with a specific impact on the detrusor function, as calcium blockers, diuretics, antihypertensive and antiarrhythmic drugs [23]. In addition, cardiovascular and psychiatric comorbidities are often associated with MS [7,10,12]. Nevertheless, psychiatric comorbidities were not very prevalent in our population, which can be explained by the fact that only active comorbidities were identified. In addition, the other studies analyzed a different population not limited to patients complaining of urinary disorders. Endocrine comorbidities may be the cause of specific urinary disorders (overactive bladder by reducing parasympathetic neurons viability). These pathologies, including dyslipidemia, were frequent in our series. Dyslipidemia is a comorbidity often found in MS, which is often increased due to the inflammatory process [7,24]. Obviously, urological comorbidities (benign prostatic hypertrophy, prolapse) induce urinary disorders but also constitute a noxious stimulus for the neurogenic bladder and thus, explaining their high incidence in our study.

**Results: association between urinary disorders and comorbidities**

Our study did not reveal a significant link between the existence of one or more comorbidities and the severity of the lower urinary disorders measured by the various USP sub-scores. Although a significant association was found between lower urinary tract symptoms and several types of comorbidities (osteoarthritis, asthma, depressive syndrome, depression, diabetes, heart failure, hypertension, overweight, metabolic syndrome) [13,14,25,26], none of them studied the impact of these pathologies on the severity of these symptoms in our population of MS patient. This fact is probably due to the importance of the neurogenic bladder in comparison with the direct effects of the different comorbidities on the urinary function. However, a significant association was found between the overweight and the urinary symptoms severity, stress urinary incontinence and voiding dysfunction. These results are consistent with those described in the literature, especially in obese men with a greater prostatic weight and obese female with a high prevalence of stress urinary incontinence. One of the advanced mechanisms in men would be the greater aromatization of testosterone into estrogens in adipose tissue leading to prostatic hyperplasia [27]. Overweight is one of the components of the metabolic syndrome, often described as associated with lower urinary disorders, via an increase in sympathetic autonomic nervous system activity and prostatic hypertrophy. These mechanisms may explain the association between metabolic syndrome, overactive bladder syndrome and voiding dysfunction [28]. As for the overweight association and stress incontinence, it has been known for a long time and has been reinforced by the improvement of the symptoms after reduction of weight [29]. There was no significant association in our study between overweight and overactive bladder, probably related to the frequency of this symptom in MS neurogenic bladder (96% of our population).

**Study limitations**

Nevertheless, there are some limitations in this work, notably the retrospective nature of the study. Moreover, neither the evolution of MS or the duration of the disease were taken into account in the analysis though these parameters have not a direct impact on urological symptoms and urodynamic conditions. In addition, patients were included regardless of the treatment of overactive bladder (anticholinergic, sacral or peripheral neuromodulation, intra-detrusor injection of botulinum toxin). We have classified comorbidities according to the ICD-10 classification [30], but the use of a comorbidity index, such as the Charlson comorbidity index, could be more appropriated for comparison with other studies [31].

An other study limitation is the use of the Urinary Symptom Profile questionnaire, which hasn’t been validated in the neurogenic bladder patients; however this score was firstly design to only describe symptoms, indeed the original article didn’t detail the patient pathologies [17].

Finally, the existence of active treatment of comorbidity was not considered even if, in some case, these treatments may affect presence, type or importance of urinary symptoms; because such selection could lead to a bias. Despite these limitations, this study seems to be relevant because of the number of patients, the full clinical (with validated questionnaires) and urodynamic assessments and the consistency of our results. Indeed, a significant relationship between overweight and USP SUI subscore is an expected result, as well as the relationship between overweight and voiding dysfunction.

**Perspectives**

Even this work did not identify a link between comorbidities and severity of urinary disorders, it allowed to show that the most prevalent comorbidities in multiple sclerosis (high blood pressure, dyslipidemia…) could also act on the bladder and create urinary disorders in addition to the neurological disease. This observation leads us to the conclusion that the comorbidities in multiple sclerosis must be searched and treated systematically. The treatment of high blood pressure, dyslipidemia or else, could be the first step of treatment for the multiple sclerosis patients with urinary symptoms, before anticholinergic drugs or botulinum toxin.

**Conclusion**

In our study, the comorbidity prevalence in MS patients is 50.9%. Cardiovascular and endocrinological comorbidities are the most frequent. No association was found between the presence of at least one comorbidity and the severity of the urinary symptoms. A significant association was found between the presence of overweight and stress urinary incontinence and voiding dysfunction.

Knowledge of these comorbidities in MS is important since the presence of urinary symptoms not related to neurogenic bladder must lead to a specific treatment (i.e. metabolic syndrome, overweight) which can improve urinary condition, decrease urological complications and improve quality of life.
Disclosure of interest

The authors declare that they have no competing interest.

References


