



Specificity of Lower Urinary Tract Symptoms in Neuromyelitis Optica in Comparison With Multiple Sclerosis Patients

Arnaud Declémy^{1,2}, Camille Chesnel^{1,2}, Audrey Charlanes^{1,2}, Frederique Le Breton^{1,2}, Samer Sheikh Ismael^{1,2}, Gerard Amarenco^{1,2}

¹GREEN GRC-01 UPMC (Group of Clinical Research in Neurourology), Sorbonne University, Paris, France

²Department of Neuro-Urology, Tenon Hospital, APHP, Paris, France

Purpose: The aim of this study was to describe lower urinary tract symptoms in neuromyelitis optica (NMO), and to compare these data with urinary disorders observed in multiple sclerosis (MS) patients.

Methods: Retrospective study of data collected from January 1997 to July 2017 using the database from a Neuro-Urology Department of a university hospital. NMO and MS patients were matched for sex, age, and Expanded Disability Status Scale (EDSS)

Results: Twenty-six patients with NMO were included and compared with 33 MS patients. Mean age was 41.6 years (standard deviation [SD], 14.8), mostly female patients (24 vs. 2 males). Mean EDSS was 4.6 (SD, 1.8) in the 2 groups. In NMO group, 57% of the patients (n = 15) had overactive bladder with urgency and urge incontinence and 38.5% (n = 10) of them had nocturia. Voiding symptoms was observed in 69.2% of the patients (n = 18); 42.3% of NMO patients performed self-intermittent catheterization versus 12.1% in MS patients (P = 0.012). Low bladder compliance and severe urinary tract infections (pyelonephritis) were more frequent in NMO than in MS patients (respectively 15% vs. 0%, P = 0.016 and 42% vs. 12%, P = 0.024).

Conclusions: Lower urinary tract symptoms, especially overactive bladder and urinary retention, are frequent in NMO. Low bladder compliance, serious urinary infections, and high prevalence of urinary retention requiring self-intermittent catheterization are the main symptoms significantly more frequent than in MS.

Keywords: Devic disease; Neuromyelitis optica; Multiple sclerosis; Lower urinary tract symptoms; Voiding disorder

- **Research Ethics:** This study was approved by the local ethics committee (Comité de Protection des Personnes Ile de France II: 00001072). Written informed consent by the patients was waived by the Institutional Review Board due to a retrospective nature of our study.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Neuromyelitis optica (NMO) or Devic disease (DD) is an autoimmune inflammatory disorder of the central nervous system. NMO is considered as a variant of multiple sclerosis (MS). This syndrome was described first by Albutt in 1870 (quoted from [1]). NMO affects preferentially the optic nerves and the spinal cord and frequently follows a relapsing course with severe disabling episodes of optic neuritis and extensive transverse myeli-

tis [2]. In 2004, a specific marker for NMO was identified, the aquaporin 4 antibody (AQP4-IgG) or NMO-immunoglobulin. The presence of AQP4-IgG in patients is associated with NMO related disorders often referred to NMO spectrum disorders (NMOSD) [3].

NMOSD is more prevalent in women than men with a sex ratio usually higher than observed in MS. The median diagnostic age is also higher than in MS, 35 MS - 45 NMO years [2,4]. Due to the treatment and prognosis differences between NMOSD

Corresponding author: Arnaud Declémy  <https://orcid.org/0000-0003-4591-4351>
Department of Neuro-Urology, Tenon Hospital, 4 rue de la Chine, 75020 Paris, France

E-mail: arnauddeclemy@free.fr / Tel: +33615632361 / Fax: +33-156017481

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and MS, it seems to be important to distinguish the 2 pathologies. The diagnosis consensus criteria for NMOSD includes at least one core clinical characteristic, a positive test for AQP4-IgG, and exclusion of alternative diagnoses [4].

Lower urinary tract symptoms (LUTS) are well known and well described in MS. The most common symptom is overactive bladder syndrome with mostly an overactive detrusor on cystometry [5,6]. In contrary, only few studies described urinary disorders in NMOSD. De Carvalho et al. [7] found a prevalence of LUTS among NMOSD patients in about 80% of the cases. The most frequent symptoms are urgency, nocturia, urinary incontinence, and voiding symptoms [8]. Furthermore, no study has compared the clinical and urodynamic characteristics between MS and NMOSD patients [7,8].

It is known that urinary complications are more serious in spinal cord injuries population [9]. Even these complications are not the main causes of mortality anymore, they are still important and need an aggressive treatment and specific follow-up [10,11]. Because severe transverse myelitis is common in NMOSD [12], it could be speculated, due to the importance of spinal lesions in the pathophysiology of bladder dysfunction, that LUTS are more frequent and more severe than in MS [13]. However, on the contrary of spinal cord injury, NMOSD is an active disease, with a progressive degradation of the functional abilities [14]. Moreover many studies have shown that the evolution of NMOSD was more pejorative than MS [15]. Because of these 2 characteristics, it seems important to evaluate prevalence, severity, urological consequences and quality of life impact of LUTS in NMOSD, in comparison with MS [16,17]. This knowledge will allow us to treat efficiently the patients.

The main aim of this study was to assess the clinical and urodynamic characteristics of urinary disorders in patients with NMOSD consulting in a Neurology department using a database. The second aim was to compare these data with those of MS patients and assess the differences between the 2 populations.

MATERIALS AND METHODS

Study Design

A retrospective study was conducted: all patients with NMOSD referred for urinary disorders in a Neuro-Urology Department of a University Hospital between January 1997 and July 2017 were included. Inclusion criteria were patients with an established diagnosis of NMOSD (clinical, and magnetic resonance

imaging [MRI] criteria before 2005 and clinical, biological and MRI criteria after 2005). Patients with MS diagnosed according to the revised criteria of Mc Donald's were identified [18].

Each patient with NMOSD was matched with at least 1 or 2 MS patients for sex, age, and according to the Expanded Disability Status Scale (EDSS) [19].

Variables

For each patient, clinical and urodynamic data were collected: age, sex, severity of neurological disability measured by the EDSS, and duration of follow-up. Patients were classified into 3 categories according to the EDSS: from 1 to 4, 4.5 to 6.5, and more than 7. The first group was patients with EDSS from 1 to 4, the second class with EDSS from 4.5 to 6.5, the third with 7 and more.

The symptoms existing during the first clinical evaluation were noted and divided between the storage symptoms such as urgency, nocturia, stress urinary incontinence (SUI), and urgency urinary incontinence; and the voiding symptoms (slow stream, intermittent stream, hesitancy, straining to void), the urinary treatments during the first clinical evaluation were also noted, as well as the use of intermittent catheter as voiding mode. The existence of urinary infection during the last year were searched with difference between urinary infection without fever and pyelonephritis

The urodynamic parameters from the first urodynamic evaluation were documented with: the existence of detrusor overactivity (phasic or terminal), the volume of the first involuntary detrusor contraction, the maximum intravesical pressure during the evaluation, the presence of a low bladder compliance (the compliance is calculated by dividing the volume change by the change in detrusor pressure during that change in bladder volume, a compliance = 20 or less is considered as low), the cystometric capacity, the presence of a detrusor sphincter dyssynergia (DSD). During the evaluation if the patient presented a post void residual of 100 mL or more, it was considered as urinary retention.

Using an echography, the presence of vesicoureteral reflux or lithiasis, as well as a renal failure on biology, was resumed in "morphological complications."

The urodynamic studies were performed according to "the Good Urodynamic Practice" recommended by the International Continence Society [20]. All definitions used were in accordance with the International Continence Society Report [21].

Statistical Analysis

Descriptive statistics were expressed as the mean \pm standard deviation (SD). Differences between groups were assessed with the Student t-test for quantitative variables and chi-square or Fischer tests for categorical variables. Statistical analyses were carried out using R software ver. 3.3 (R Foundation for Statistical Computing, Vienna, Austria) with a $P < 0.05$ considered significant.

Ethics

This study was approved by the local ethics committee (Comité de Protection des Personnes Ile de France II: 00001072). 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

Clinical and Urodynamic Characteristics of NMOSD Population

Twenty-six patients with NMOSD were included with a mean age of 41.6 years (SD, 14.8). Most of the patients were women (93.9%, $n = 24$ patients). Only 2 patients had an EDSS higher than seven. 57.7% ($n = 15$) of the patients had urgency, 57.7% ($n = 15$) urge incontinence, 26.9% ($n = 7$) SUI, and 38.5% ($n = 10$) had nocturia. Voiding symptoms was observed in 69.2% of the patients ($n = 18$), and 42.3% used self-intermittent catheterization as voiding mode. The duration of follow-up in NMOSD population was 8.2 years (SD, 7.8).

Nine NMOSD patients were treated by means of anticholinergic drugs (34.6%), 6 received alpha-adrenergic blocking drug (23.1%), and 2 used botulinum toxin A injections in detrusor (7.7%) in as-

Table 1. Comparison of demographic and clinical characteristics of LUTS in the 2 population

Variable	MS (n = 33)	NMOSD (n = 26)	Total (n = 59)	P-value
Demographic characteristic				
Age (yr) ^{c)}	40.2 \pm 15.8	41.6 \pm 14.8		0.734
Female sex ^{b)}	31 (93.9)	24 (92.3)	55 (93.2)	0.804
Duration of follow-up (yr) ^{c)}	12.6 \pm 10.6	8.23 \pm 7.84		0.071
EDSS ^{a)}				
< 4	16 (48.5)	13 (50)	29 (49.2)	0.858
4.5–6.5	13 (39.4)	11 (42.3)	24 (40.7)	
≥ 7	4 (12.1)	2 (7.7)	6 (10.2)	
Disease modifying treatment ^{b)}	20 (60.6)	14 (53.8)	34 (57.6)	0.862
Urinary symptomatology				
SUI ^{a)}	8 (24.2)	7 (26.9)	15 (25.4)	0.789
Urgency ^{a)}	22 (66.7)	15 (57.7)	37 (62.7)	0.479
Urgency urinary incontinence ^{a)}	19 (57.6)	15 (57.7)	34 (57.6)	0.992
Nocturia ^{a)}	17 (51.5)	10 (38.5)	27 (45.8)	0.285
Voiding symptoms ^{a)}	26 (78.8)	18 (69.2)	44 (74.6)	0.353
Catheterization ^{a)}	4 (12.1)	11 (42.3)	15 (25.4)	0.012*
Infection ^{a)}	9 (27.3)	12 (52.2)	21 (35.6)	0.063
Infection with fever ^{a)}	2 (6.1)	7 (26.9)	9 (15.3)	0.024*
Bowel symptomatology				
Constipation ^{a)}	21 (63.6)	16 (61.5)	37 (62.7)	0.977
Anorectal dyschezia ^{a)}	19 (57.6)	14 (53.8)	33 (56.0)	0.904
Fecal incontinence ^{a)}	1 (3.0)	1 (3.84)	2 (3.4)	1.000
Sexual symptomatology				
Dyserection ^{a)}	0 (0)	0 (0)	0 (0)	
Dysejaculation ^{a)}	0 (0)	1 (3.84)	1 (1.7)	0.807
Urinary treatment				
Anticholinergic ^{a)}	10 (30.3)	9 (34.6)	19 (32.2)	0.725
Alpha adrenergic blocking drug ^{a)}	10 (30.3)	6 (23.1)	16 (27.1)	0.535
Botulinum toxin ^{a)}	1 (3.0)	2 (7.7)	3 (5.1)	0.577

Values are presented as mean \pm standard deviation or number (%).

LUTS, lower urinary tract symptoms; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; EDSS, expanded disability status scale; SUI, stress urinary incontinence; Anticholinergic, anticholinergic drug.

* $P < 0.05$. ^{a)}Fisher test. ^{b)}Chi-square test. ^{c)}Student t-test.

Table 2. Comparison of urodynamic characteristics in the 2 population

Variable	MS	NMOSD	Total	P-value
Overactivity detrusor ^{b)}	16 (48.5)	12 (46.1)	28	0.663
Volume contraction detrusor ^{c)}	214.7 ± 153.8	190.8 ± 130.3		0.648
Cystometric capacity ^{c)}	367.4 ± 152.7	356.3 ± 140.4		0.783
Detrusor pressure ^{c)}	56.1 ± 33.3	54.6 ± 24.7		0.947
Low bladder compliance ^{a)}	0 (0)	4 (15.4)	4	0.016*
Detrusor sphincter dyssynergia ^{a)}	22 (66.7)	10 (38.4)	32	0.118
Urinary retention ^{a)}	19 (57.6)	11 (42.3)	30	0.433
Morphological complication	0 (0)	0 (0)	0	-

Values are presented as number (%) or mean ± standard deviation.

MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

*P < 0.05. ^{a)}Fisher test. ^{b)}Chi-square test. ^{c)}Student t-test.

sociation with self-intermittent catheterization (Table 1).

Concerning urodynamic data, 12 patients had detrusor overactivity (46.1%) and the mean cystometry capacity was 356.3 mL (SD, 140.4). Ten patients had DSD (38.4%) and 4 patients (15.4%) had a low bladder compliance (Table 2).

Comparison Between MS and NMOSD Populations

Mean EDSS was 4.6 (SD, 1.8) in the 2 groups. Febrile urinary tract infection (pyelonephritis and prostatitis) were significantly higher in the NMOSD population than in MS patients (30.4% vs. 6.1%; P=0.024). Low bladder compliance was more frequent in NMOSD patients than in MS (15.4% vs. 0% P=0.016). Voiding symptoms with significant postvoid residual volume requiring self-intermittent catheterization was more frequent in NMOSD patients than in MS (42.3% vs. 12.1%; P=0.012).

A comparison between the patients with a low bladder compliance and the others, showed a significative increase of the pyelonephritis incidence in the group “low bladder compliance” (50.0% vs. 12.5%, P=0.038).

The existence of a DSD was significantly associated with the presence of voiding symptoms (87.5%, n=28, P=0.033) and urgency urinary incontinence (59.4%, n=19, P=0.743). There was not any strong association between DSD and low bladder compliance (3.4%, n=1, P=0.475) or pyelonephritis incidence (6.2%, n=2, P=0.052)

There was no other significant difference concerning clinical or urodynamic characteristics between NMOSD and MS populations.

DISCUSSION

This article is to our knowledge, the first comparing the LUTS between NMOSD and MS patients. Our results suggest a high prevalence of urinary symptoms in NMOSD especially overactive bladder syndrome and voiding symptoms. Despite the fact that NMOSD is usually described as a neurological disease very close to MS, we found important significant differences between NMOSD and MS patients. The main difference was the more importance of urinary retention and thus the use of catheterization, the high prevalence of low bladder compliance, and high incidence of febrile urinary tract infections. These characteristics suggest a higher risk of urinary complications in NMOSD than in MS patients since low bladder compliance, recurrent urinary tract infections, and postvoid residual volume are well known to lead to renal complications and failure. These data suggest the need to track down urinary disorders in NMOSD patients with a systematic proposal of a specific periodic follow-up to decrease these risks and to improve quality of life.

Interpretation of Results

The NMOSD is a chronic inflammatory disease that affects the central nervous system and which seems to be very close of MS. But in fact, there are several characteristics that differentiate MS and NMOSD:

- The evolution of NMOSD is more pejorative than MS [15].
- Some treatments used in MS, did not work on NMOSD patient [22].
- NMOSD has a lower incidence than MS [23].

As there were differences between NMOSD and MS, we sup-

posed that urinary disorders were different in both diseases. The initial speculation was that NMOSD had more urologic complications (pyelonephritis, vesicoureteral reflux, or renal failure, ...).

This supposition was based on several arguments:

- Myelitis is common in NMOSD, and it's well known that urinary complications are more serious in spinal cord injury [9].
- NMOSD is an active disease with pejorative evolution leading to a degradation of the voiding control (on the contrary of spinal cord injury).
- NMOSD is often confused with MS, leading to lack of data on urinary disorders in this specific disease.

Our results confirm that there was more pyelonephritis and low compliance bladder in NMOSD group. These results seem to confirm that the urinary disorders are more severe in NMOSD patients than MS patients.

As we already say NMO is an active disease like MS, but with spinal injury (myelitis). In other terms, NMO combine the more serious urinary complication (because of myelitis), and the progressive degradation of neural voiding control (like MS). With this observation, we understand that we cannot applied a similar medical reasoning than MS or spinal cord injury.

We propose that every patient with NMOSD diagnosis is referred to Neuro-Urology Department event no specific urinary symptom is observed. The follow-up for these patients should be the same than spinal cord injury patients: over a 2 years period, at 6-month intervals at the beginning and then every year in order to monitor the neurological degradation. As a same way the treatment proposed needs to be more aggressive early. The treatment must be re-evaluated for each step of functional loss.

Comparison With Literature

Characteristics of our population in term of urinary disorders are similar to 2 previous studies concerning urinary function in NMOSD. The first one reported the prevalence of LUTS in a population of NMOSD followed prospectively and showed that most of these patients had significant LUTS including urgency, nocturia, and voiding symptoms. The most frequent urodynamics findings were DSD (present in over half of the patients) and overactive bladder [7]. The authors suggested that DSD was the most common urodynamic abnormality in NMOSD, in contrast with MS. On the contrary, in our study, there is no significant difference between MS and NMOSD patients concerning prevalence of overactive bladder and/or DSD. The sec-

ond study was a cross-sectional study, investigating the bowel and bladder dysfunction and their impact on quality of life in 60 NMOSD patients. In this article, 78% patients reported bladder symptoms, 60% had urgency, 47% had incontinence, and 39% had nocturia. Moreover, 45% of the patients had a moderate or severe bowel problem, 79% were constipated and 23% had fecal incontinence [8]. In our study, we observed the same prevalence of overactive bladder symptoms (urgency [57.7%], urge incontinence [57.7%], nocturia [38.5%]) but voiding symptoms was more frequently observed (69.2%) than in the previous studies. Similarly, we found a high prevalence of constipation (64%).

Limitations of the Study

Nevertheless, there are some limitations in this work, the most important is the retrospective nature of this study. This retrospective nature leads to several biases, such as memory or selection biases, inducing a lack of power. Moreover because of the specialization of our department, we create a selection bias; because our patients are consulting for LUTS. However, this expertise allowed us to find a cohort of 26 patients with NMOSD, which is a consequent population because of the illness rarity, comparing to MS [24].

In conclusion, to our best knowledge, we report here the first clinical and urodynamic comparison between NMOSD and MS patients. We found a significant difference between the 2 populations, concerning the prevalence of febrile urinary infections, the importance of voiding dysfunction and urinary retention requiring the use of self-intermittent catheterization, and presence of low bladder compliance in NMO. Despite the limitations of our study due to retrospective analysis, we can suggest that the LUTS observed in NMOSD are more important than in MS and can lead to more severe complications. A further and prospective study could demonstrate a possible difference in term of efficacy concerning the specific urinary treatment.

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AUTHOR CONTRIBUTION STATEMENT

- Full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis: *AD*
- Study concept and design: *GA, AD*
- Acquisition of data: *AD*
- Analysis and interpretation of data: *CC, AD*
- Drafting of the manuscript: *GA, CC, AD*
- Critical revision of the manuscript for important intellectual content: *GA, CC, AC, FL, SS*
- Statistical analysis: *CC, AD*
- Administrative, technical, or material support: *GA*
- Study supervision: *GA*

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