Lower Urinary Tract Dysfunction in Patients with SMON (subacute myelo-optico-neuropathy)

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Abstract
The relation between disturbance of activities of daily living and lower urinary tract dysfunction estimated by the International Prostate Symptom Score was examined in 66 patients with subacute myelo-optico-neuropathy (SMON). Forty-three patients (65%) were considered to have symptomatic lower urinary tract dysfunction. Storage urinary symptoms correlated significantly with the severity of gait disturbance in SMON patients, especially in female patients, suggesting that lower urinary tract dysfunction originates in the spinal cord as damage by clioquinol intoxication. In male patients, voiding symptoms also correlated with the Barthel Index and gait disturbance. However, since voiding symptoms tended to be correlated with age in male patients, these symptoms may be associated with age-related development of bladder outlet obstruction, such as benign prostatic hyperplasia.

Key words Clioquinol, Clinical study, Voiding dysfunction, SMON

Introduction
Subacute myelo-optico-neuropathy (SMON) is a disease caused by clioquinol intoxication, characterized by the subacute onset of sensory and motor disturbance in the lower extremities, with visual impairment following abdominal symptoms, mainly occurring during the 1950–60’s in Japan.1,2 The pathological features are characterized by system degeneration of the long tracts of the spinal cord combined with polyneuropathy and optic nerve involvement.3 After banning the sale of drugs containing clioquinol in September 1970, a sharp decrease in the number of SMON patients was observed in Japan. It is estimated that the number of SMON patients slightly exceeded 3,000 in 2002 and mean age of 1,031 SMON patients exceeded 70 years old (mean age + SD, 72.9 ± 9.6) with a female predominance (male: female; 1: 2.75).4 The mean age of SMON patients in Japan has constantly increased due to an absence of new patients with SMON.

From a nationwide survey of 419 SMON patients by the SMON Research Committee, the prevalence of urinary incontinence increased from 3.3% always and 34.6% sometimes in 1990 to 6.2% and 54.2%, respectively, in 2000.5 Urinary complications severely disturb the patient’s activities of daily living. Sensory and motor disturbance in SMON may cause some types of neurogenic bladder dysfunction. However, the prevalence of lower urinary tract dysfunction (LUTD) also increases with age. Thus, it is unclear whether LUTD in SMON patients occurs simply due to aging or is related to neural lesions in SMON.

To examine this problem, LUTD in SMON patients was characterized using severity scales and age. The International Prostate Symptom Score (I-PSS) was originally used for quantitative evaluation of subjective lower urinary tract...
symptoms (LUTS) in benign prostatic hyperplasia. Subsequently, this procedure was extended to evaluate LUTS in various conditions in men and women. Since the I-PSS questionnaire includes particular questions on storage and voiding urinary symptoms, both of these types of urinary symptoms can be separately examined. Previous studies by this group indicated that LUTS quantified by I-PSS reflects well the urodynamic abnormalities in central nervous system diseases, such as Parkinson’s disease and multiple sclerosis.

Materials and Methods

Using I-PSS, lower urinary tract dysfunction (LUTD) was evaluated in 66 patients (17 males, 49 females, ranging from 49 to 96 years of age (mean, 72.2)) with SMON living in Kyoto Prefecture, Japan, in 2000. The duration of SMON disease was 33.2 ± 2.4 years (mean ± SD), and the range was 30 to 41 years. Clinical symptoms of SMON were evaluated using medical checkup records established by the SMON Research Committee. Because each questionnaire was answered by the patients themselves or by their relatives without the aid of neurologists or urologists, there may exist some uncertainty of clinical evaluation of SMON patients. In each patient, the total scores for the Barthel Index were calculated. Gait scores were obtained from the severity of gait disturbance. The severity of gait disturbance was classified into 5 grades as follows: bed-ridden, able to move using a wheelchair, able to walk with aid on a flat area, able to walk without aid except up stairs, able to climb stairs without aid. SMON patients with severe complications such as cerebrovascular disease, disease of the peripheral nervous system or dementia were excluded from this study.

The I-PSS questionnaire comprises 7 questions on LUTSs and additional questions on general satisfaction with the urinary condition. Frequency, urgency and nocturia may reflect the state of storage symptoms (maximal score 15), whereas incomplete emptying, intermittency, weak stream and staining at the beginning of urination may be indicative of voiding symptoms (maximal score 20). In addition to these questions, urinary incontinence, sleep condition and desire for therapy for urinary disturbance were included.

Among nonparametric analyses, Spearman’s rank correlation coefficients were calculated between variables. All P-values presented are 2-tailed. P < 0.05 was considered statistically significant. Multiple regression analyses with forward regression and with backward elimination were conducted to assess the independent association of age, gender, Barthel Index and severity of gait disturbance with the storage or voiding symptom scores. The inclusion or elimination thresholds were P < 0.05.

Results

Arbitrarily, patients with a symptom index score of 12 or higher were considered to have symptomatic voiding dysfunction. With this criterion, 43 patients (65%) were found to be symptomatic. When the score for storage symptoms or voiding symptoms was >7 or >9, patients were considered to be symptomatic. Eleven patients (17%) had storage symptoms alone, and 8 patients (12%) had voiding symptoms alone. Twenty-six patients (39%) manifested both types of symptoms.

Urinary incontinence was observed in 18 patients (27%) and sleep disturbance due to frequent nocturia was observed in 34 patients (55%). Fourteen (24%) out of 56 patients wanted medical treatment for their urinary disturbance. Correlations between the I-PSS score and age, and the Barthel Index score and severity of gait disturbance were examined in all patients and in each sex (Table 1). In all SMON patients, the I-PSS scores significantly correlated with the Barthel Index and gait scores (P < 0.05). Each parameter of the Barthel Index was not correlated with the I-PSS score. In female SMON patients, severity of gait disturbance was significantly correlated with the storage symptom scores. The age of female SMON patients was correlated with neither the total scores, the storage scores nor the voiding symptom score. In male SMON patients, the Barthel Index and gait scores were significantly correlated with the total urinary symptom scores, and with the voiding symptom scores. As in female SMON patients, severity of gait disturbance was significantly correlated with the storage symptom scores. The age of male SMON patients tended to be correlated with the total scores and the voiding symptom scores but was not significant.
Multiple regression analyses with forward regression and with backward elimination showed that female and older-age-group patients with low Barthel Index scores under 50 points were important factors influencing the storage symptom score. However, no significant factors that influence the voiding symptom score were clarified.

Discussion

In a nationwide survey of SMON patients in Japan in 2002, complications were present in 93% of 1,032 SMON patients and were mostly geriatric problems, such as cataract, hypertension, vertebral disease, limb articular disease, digestive dysfunction, heart disease and bone fractures. Incontinence of urine was seen in 60.7% and of feces in 32.7%. Incontinence of urine was seen in 60.7% and of feces in 32.7%.

Using the I-PSS questionnaire, more than a half the SMON patients (65%) were found to have LUTD, as evaluated by I-PSS. This high percentage was compatible with the percentage complaining of urinary incontinence, obtained from a nationwide survey of SMON patients in Japan in 2000, in which the prevalence of “urinary incontinence sometimes” was 54.2%. From the results of I-PSS applied to SMON patients, storage symptoms correlated with disability of motor function of the lower extremities examined using both nonparametric and multiple regression analyses, suggesting that storage symptoms in SMON patients are caused by spinal cord lesions from intoxication with clinoquinol. Multiple regression analyses suggested that female and older-age-group patients with lower Barthel Index scores were important factors for evaluating the storage symptom scores. The spinal cord origin of LUTD in SMON indicated by our study is compatible with the results of urodynamic studies for 6 patients with SMON, in which supranuclear pelvic nerve dysfunction was suggested to be mainly responsible for the micturitional disturbance.

The reported increase in the prevalence of urinary incontinence over the last 10 years may reflect the increase in the mean age of SMON patients, with no new SMON patients reported since 1970. The prevalence of lower urinary tract symptoms in Asian men showed an increase in all symptom scores of IPSS with advancing age. The scores in subjects aged 70 to 79 years were approximately twice those of subjects aged 40 to 49. In male patients, the gait scores significantly correlated with voiding symptoms as well as storage symptoms. However, voiding symptoms showed some correlation with age, suggesting that the urinary symptoms in male patients were caused at least partly by age-related infravesical obstruction (i.e. benign prostatic hyperplasia). The presence or absence of prostatic hypertrophy in male patients was not clear in this study due to a lack of correlation.

<table>
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<tr>
<th>Table 1</th>
<th>Spearman’s rank correlation coefficient between the I-PSS score and age, plus the Barthel Index score and severity of gait disturbance in all patients and in each sex</th>
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<td>Severity of gait disturbance</td>
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<td>Female patients (49)</td>
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<td>Male patients (17)</td>
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*: P<0.05, **: P<0.01
of precise urological investigations. The pathophysiological differences between male and female SMON patients are not clear in this study due to the age factors especially observed in male patients and a lack of precise urodynamic study of each patient. Similar studies during or just after clioquinol intoxication would be useful for clarifying the effects of clioquinol on the autonomic nervous system including urinary functions and sex differences.

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References