Radiopaque Markers Transit and Anorectal Manometry in 16 Patients with Multiple Sclerosis and Urinary Bladder Dysfunction

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Fecal incontinence and/or constipation are frequent complaints in multiple sclerosis associated with urinary bladder dysfunction, incontinence, and/or retention. Total and segmental colonic transit were studied by determination of radiopaque markers, and anorectal function by anorectal manometry, in 16 multiple sclerosis patients clinically defined (with urinary bladder dysfunction shown by urodynamic examination). Fifteen multiple sclerosis patients had constipation and 14 had increased colonic transit time; ten multiple sclerosis patients had fecal incontinence and five had spontaneous rectal contractions. It is suggested that increased colonic transit and anorectal dysfunction were secondary to neurologic disorders just as urinary bladder dysfunction is due to neurologic disorders in multiple sclerosis. [Key words: Multiple sclerosis; Colonic transit; Anorectal manometry]

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CONSTIPATION IS A frequent clinical complaint by patients with multiple sclerosis; 39[1] to 53 percent[2] of multiple sclerosis patients complain of constipation, most often with concomitant urinary disorders.[1,2] Regardless of the origin of the constipation, it is due to a decreased rate of transit whose site may be colonic (right colon, left colon, or both) or distal (sigmoid flexure).[3,4]

The first aim of this study was to objectively measure colonic transit and thereby verify the constipation clinically reported by multiple sclerosis patients, and define the site of decreased transit by examining transit times of radiopaque markers.[5] The second aim was to compare anorectal and urinary bladder anomalies in the multiple sclerosis patients. The association of urinary disorders with digestive diseases in multiple sclerosis patients suggests that the same neurologic mechanism is responsible for both symptoms.[6] The neurologic origin of urinary bladder dysfunction has been shown[7,8] and the pathophysiologic mechanism most often responsible for poor bladder emptying is the existence of a detrusor urethral dyssynergia, as shown by urodynamic examination.[9] Thus, the third aim of this work was to use anorectal manometry to detect the existence of rectoanal dyssynergia, the cause of poor rectoanal emptying.

Patients and Methods

Sixteen patients with clinically defined multiple sclerosis[10] were included. There were ten women and six men with a median age of 41 years (range, 24 to 60 years). All consulted initially for urinary problems and were examined with the following protocol:

A standardized questionnaire containing (in terms of urination) the existence of urgent urination with or without incontinence, and the existence of dysuria with or without chronic or acute retention was completed. In terms of constipation, the number of weekly stools, the need for urgent defecation, the existence of evacuation difficulties, special maneuvers, use of laxatives, persistence of the sensation of need after defecation, the presence

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of hard stools with or without the coexistence of a fecaloma were recorded.

Perineal examination included the study of proprioceptive sensitivity of metamers S_2, S_3, S_4, S_5, a study of the bulbocavernous or clitoroanal reflex, and a study of the proprioceptive anal reflex.

Urologic examination included assays of blood urea and creatinine, urinalysis and urine culture, intravenous urography with permicturitional cystography and/or cystoscopy, and urodynamic examination.

Digestive examination was included, along with anorectal manometry, and measurement of transit times of radiopaque markers.

Urodynamic examination was performed in the gynecologic position, described previously.[11] The volumes of appearance of the first need (B1), the permanent need (B2), and the urgent need (B3) were noted. The occurrence of bladder contractions greater than 15 cm of water were noted during filling, whether or not accompanied by the sensation of need. Bladder and urethral pressures during micturition were recorded by external fixation of the probe at the level where maximal urethral profile pressure was recorded with a filled bladder. The micturitional volume and postmicturitional residue were measured. The presence of detrusor urethral dyssynergia in the 16 patients was determined by: 1) the presence of a residue greater than 20 percent of micturition in the absence of a urethral mechanical obstruction, and/or 2) the existence of a bladder/urethral pressure gradient less than 10 cm of water during micturition in spite of a bladder contraction greater than 40 cm of water. Detrusor urethral dyssynergia was confirmed in eight patients by recording the electromyographic activity of the perineum, showing either the absence of a decrease or the increase of this activity during micturition.[12,13]

Transit times of radiopaque markers were measured. At the time this examination was performed, patients were receiving no medication known to modify the functioning of smooth digestive muscle. They were on a normal uncontrolled diet, especially in terms of the supply of alimentary fibers. The examination was performed as described by Arhan *et al.*[5] Patients ingested 20 radiopaque markers in a single dose and had abdominal X-rays without preparation every 24 hours for five days. The number of markers in the right colon, left colon, and sigmoid flexure was counted on each film and segmentary and total transit times were calculated. If markers persisted on the last film, it was admitted that they disappeared 24 hours later and, in this case, transit time was considered to be equal to, or greater than, that calculated.[11]

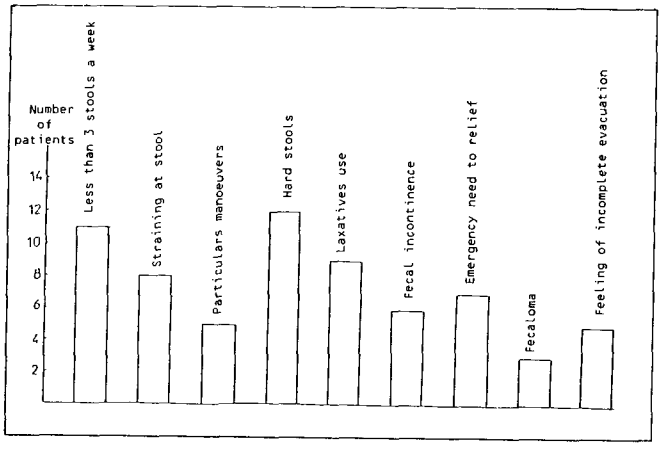

FIG. 1. Distribution of digestive complaints among the 16 patients with multiple sclerosis.

The results obtained with the 16 multiple sclerosis patients were compared to those obtained with 20 volunteers (ten men, ten women), with a median age of 29 years (range, 17 to 40 years) who were also on a normal uncontrolled diet.

Anorectal Manometry was done as described by Martelli *et al.*[14] A balloon probe was used. Ahead of the distending balloon were two 1-cm in diameter recording balloons, 1.5 cm apart. The probe was placed so that the most external balloon was in the lower part of the anal canal. Under these conditions, the second balloon was in the upper part of the canal and the distending balloon was in the lower part of the rectal ampulla. Pressures were recorded with electromanometers (Statham P23 ID) and manometry included four successive steps as described previously.[11] Results of rectoanal manometry were interpreted as a function of those obtained with 17 volunteers (11 men, six women), median age 24 years (range, 20 to 29 years). As observed by others,[3,4] the authors considered that one or more of the following anomalies defined the pattern of constipation as resulting from an outlet obstruction: hypertonia in the upper part of the anal canal with or without ultraslow waves greater than 20 cm of water; the presence of an overshoot after rectoanal inhibitor reflex (RAIR); RAIR absent or amplitude insufficient.

Statistical Analysis of quantitative variables was carried out with the Student's *t*-test.

Results

Urinary and Digestive Symptoms: All patients presented with urinary symptoms including incontinence (14 cases) and/or retention (11 patients). Results of the questionnaire dealing with digestive complaints are shown in Fig. 1. One patient did not complain of constipation. Constipation appeared before (three cases), at the moment of (two cases), or after (ten cases) the first episode of multiple sclerosis, and before (six cases), at the moment of (four cases), or after (five cases) the appearance of urinary symptoms.

Perineal Examination: Perineal reflexes were judged

excessive in 12 patients with hypoesthesia of the perineum (two cases). The examination was normal in four patients.

Urologic Examination: Blood urea and creatinine were normal in all patients. Intravenous urography showed no renal anomalies, but a postmicturitional residue was noted in 13 patients. All urines were sterile at the moment of urodynamic examination.

Urodynamic Examination: All urodynamic examinations were abnormal. Twelve patients had hyperreflexia of the urinary bladder. In 11, the need to urinate progressed regularly from B1 to B3. Four patients immediately felt an urgent need and one patient felt no need in spite of a 500 ml filling volume. The urethral profile pressure was normal in 15 patients and was 115 cm of water in one (46-year-old woman in whom it was the only urodynamic anomaly). Finally, there was detrusor urethral dyssynergia in 14 patients.

Transit of Radiopaque Markers: Transit times were normal in two multiple sclerosis patients. There was increased transit time involving only the right colon in three patients, the left colon in two, and the sigmoid flexure in three. Increased transit time coexisted in the right and left colon in three patients, in the left colon and sigmoid flexure in two patients, and in all colonic segments in one. Comparison of the mean transit time of each colonic segment in multiple sclerosis patients and control subjects is shown in Fig. 2.

Anorectal Manometry: The mean functional length of the anal canal in multiple sclerosis patients was no different from that of control subjects. Spontaneous rectal contractions were noted in five multiple sclerosis patients,

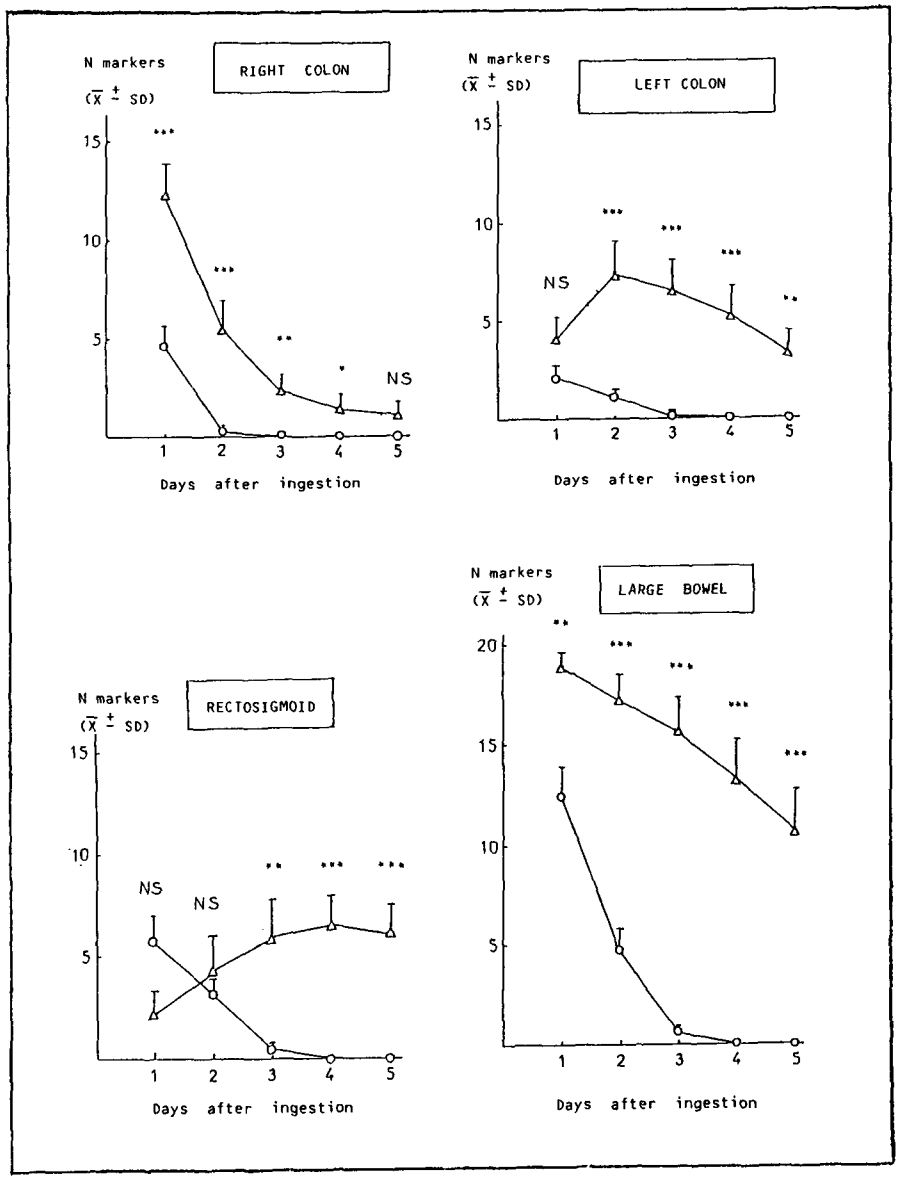

FIG. 2. Distribution of radiopaque markers during transit through the large bowel. Average number of markers present in the different segments of the large bowel after the ingestion of 20 markers. Triangles: multiple sclerosis. Circles: healthy controls. $*P<0.05$. $**P<0.01$. $***P<0.001$. $\bar{x}$ = mean, SD = standard deviation.

but in no control subjects. Ten multiple sclerosis patients manifested the manometric anomalies of an "outlet obstruction" defined under "Methods": in five cases the RAIR amplitude was diminished for all volumes of rectal distention; the pressure was too high in the upper part of the anal canal in one case, and in the lower part of the anal canal in four cases (in one of these cases, the pressure was too high in the upper and lower part, and the RAIR amplitude was insufficient); in two cases there were only ultraslow waves (one case), or overshoot after the RAIR (one case). The perception threshold of rectal distention was normal (< 20 ml) in 11 cases, increased in five (three cases of perception for 30 ml of distention, two cases for 50 ml). The mean amplitude of initial contraction in the lower part of the anal canal for each rectal distention volume, as well as the amplitude and mean duration of the anus in control subjects and multiple sclerosis patients, are shown in Table 1. In multiple sclerosis patients the amplitude and duration of the voluntary anal contraction were insufficient, and in six patients, it was the only anorectal manometric anomaly.

Correlation Between Urinary and Digestive Symptoms: Seven multiple sclerosis patients had need for emergency relief, and also had need for emergency micturition. Six multiple sclerosis patients had fecal incontinence, and five of them also had urinary incontinence.

Correlation Between Digestive Symptoms and Digestive Investigations

Transit of Radiopaque Markers: One multiple sclerosis patient with no digestive symptoms had an increased right colonic transit, and one multiple sclerosis patient with normal transit time complained of constipation (less than one stool per week). Thirteen of the 14 multiple sclerosis patients with increased transit times complained of constipation (less than three stools per week and/or straining at stool). Five of the eight multiple sclerosis patients with straining at stool had increased transit times in the sigmoid flexure, and three had increased transit times in the left colon.

Anorectal Manometry: Six of the eight multiple sclerosis patients with straining at stool manifested manometric anomalies of an outlet obstruction (anal canal hypertonia, four cases; amplitude of RAIR insufficient, two cases). Five of the six multiple sclerosis patients with fecal incontinence had spontaneous rectal contractions, and three of them had abnormal threshold perception of rectal distention.

Discussion

Digestive symptoms were noted in 15 of the 16 multiple sclerosis patients, *i.e.*, a much higher frequency than normally reported. Miller *et al.*[1] reported that 39 percent of multiple sclerosis patients complained of constipation and Sullivan and Epers[2] reported 53 percent constipation in 34 multiple sclerosis patients. In both studies, the authors noted a correlation between the presence of digestive disorders and urinary bladder dysfunction. Since the present study included patients with clinically defined multiple sclerosis with clinical urinary signs, it was logical to encounter the same correlation in the 16 patients studied. This inclusion bias was necessary because the aim was to compare pathophysiologic mechanisms of urinary and digestive disorders.

Urinary symptoms were incontinence and/or retention, and digestive symptoms were fecal incontinence and constipation, suggesting the same neurologic origin for both symptoms. Constipation is a frequent digestive complaint so that a nonneurological cause of the constipation of the multiple sclerosis patients cannot be excluded. At the onset of multiple sclerosis, however, 13 of the 16 multiple sclerosis patients were not constipated, constituting a clinical argument favoring the neurologic origin of the disorder.

The mechanism of the constipation was investigated by comparison to control subjects, whose mean ages were lower than those of the multiple sclerosis patients. This comparison was possible nevertheless because it has been shown that there are no significant age-related differences in the results for both transit times of radiopaque markers[5] and anorectal manometry.[15] In addition, the results obtained with the controls for the transit times of radiopaque markers and anorectal manometry were the same as those reported by other authors[14] using the same examination techniques. In these conditions, a comparison of the results between the two groups appeared possible.

TABLE 1. *Results ($\bar{x} \pm 1$ SEM) of Initial and Voluntary Contraction of the Lower Part of the Anal Canal in Healthy Subjects and Patients with Multiple Sclerosis.*

	Initial Contraction during RAIR				Voluntary Contractions		
	10 ml	20 ml	30 ml	40 ml	50 ml	Amplitude	Duration
Healthy subjects	22.7 ± 8.6	29.8 ± 6.3	35.0 ± 6.9	39.9 ± 6.3	35.8 ± 5.7	105.0 ±7.2	59.5 ± 3.1
Multiple Sclerosis	4.8 ± 1.7*	7.0 ± 1.7†	6.2 ±1.5†	9.4 ± 2.8†	17.5 ± 5.6*	49.7 ± 7.5†	33.1 ± 3.5†

*$P < 0.05$.
†P 0.001.
RAIR: rectoanal inhibitory reflex.

The investigation of transit times of radiopaque markers led to an objective confirmation of constipation in 13 of the 15 subjects who had clinical complaints. Colonic motility is controlled by the extrinsic nervous system because subjects with a spinal section exhibit a decrease (cephalic lesion) or an increase (caudal lesion) of colonic motility as investigated by sigmoid manometry.[16] In four subjects with lesions of the terminal spinal cord or cauda equina, Devroede *et al.*[17] also noted a decrease in the transit of radiopaque markers, with primary localization in the left colon. This also was noted in one woman with multiple sclerosis who had undergone a section of the erigentes nerves.[18] Finally, Glick *et al.*,[6,19] in a study of seven patients with multiple sclerosis and nine subjects with complete spinal section, showed a decrease in colonic compliance, and the absence of an increase of electric activity and postprandial colonic motility (these anomalies did not have a myogenic origin, since they were corrected by the injection of neostigmine).

The right colon received sympathetic innervation from the dorsolumbar spinal cord via the superior mesenteric ganglion, and vagal parasympathetic innervation. The left colon receives sympathetic innervation from the dorsolumbar spinal cord via the inferior mesenteric ganglion, and parasympathetic innervation from the sacral spinal cord via the erigentes nerves. The separation between the two types of innervations has never been defined, but it would seem logical to envision the necessity for coordination between spinal control and medullary control by the spinal pathways. Interruption of these pathways by multiple sclerosis lesions could explain the decreased transit observed in multiple sclerosis. Nervous control could be disturbed even at the pontine level, since decreased right or left colonic transit in cases of pontine lesions has been observed.[11]

Decreased colonic transit was localized in the sigmoid flexure in six patients (isolated in three), suggesting that there was also a rectoanal dysfunction in multiple sclerosis. Anorectal manometry enabled rectoanal functioning to be investigated. Eleven of the 16 multiple sclerosis subjects exhibited one or more manometric anomalies typical of the outlet obstruction described by Martelli *et al.*,[3] and confirmed in a study of 200 constipated subjects, where these anomalies were encountered in 112 cases.[4] In multiple sclerosis, as well as in idiopathic constipation, these manometric anomalies, in particular the hypertonia, are not specific, since they also existed in 50 percent of patients with inflammatory bowel disease.[4] Thus, it is not possible to determine if the observed anal hypertonia was the cause or effect of the constipation. Nevertheless, the multiple sclerosis patients exhibited two categories of anorectal manometric anomalies: 1) Five patients had spontaneous rectal contractions with clinical fecal incontinence. Urinary incontinence in multiple sclerosis is due to disinhibited detrusor contractions,[1,7-9] *i.e.*, detrusor hyperreflexia. That urodynamic anomaly was noted in 12 of the multiple sclerosis patients. The authors suggest that the same neurologic mechanism would be possible at the origin of both clinical symptoms. 2) Five patients had abnormal RAIR, suggesting an inadequacy between rectal stimulation and the anal response during RAIR.

These results suggest the existence of rectoanal dyssynergia, the mechanism of which is similar to that of dyssynergia of striated urethral muscle, *i.e.*, an excessively rapid closing of the anal canal. This rectoanal dyssynergia could be the cause of rectal evacuation problems, just as detrusor urethral dyssynergia is most often the cause of bladder emptying disorders.[8,9] It is known that detrusor urethral dyssynergia is due to a disturbance of the central neurologic control of bladder sphincter function, explaining the high frequency in multiple sclerosis patients (14 of 16 subjects). In a similar manner, a disturbance of the central neurologic control of rectoanal function, responsible for rectoanal dyssynergia, may be imagined. In four patients with involvement of the terminal spinal cord, or cauda equina, where the central neurologic control was suppressed, Devroede *et al.*[18] encountered the same RAIR anomalies. In one case of anterior pontine involvement, the absence of RAIR was noted,[11] suggesting the importance of this zone in the nervous control of rectoanal function. As is the case for the bladder, there would thus exist spinal centers controlling rectoanal function, with coordination occurring at a supraspinal level. This would explain why multiple sclerosis lesions disseminated in the spinal cord and the brain stem can disturb this control.

An electromyographic study of the striated anal sphincter was not performed; therefore it is not known if the rectoanal dyssynergia was due to a smooth or striated anal sphincter dysfunction. Nevertheless, the decreased amplitude of reflex anal contraction in the lower part of the anal canal in the 16 multiple sclerosis patients (where the striated sphincter predominates) and the decreased amplitude and duration of voluntary anal contraction suggest a dysfunction of the striated anal sphincter of the same type as the dysfunction of the urethral sphincter. In neurologic constipation, it is possible that the dysfunction of the striated sphincter is due to a disturbed coordination between the reflex rectoanal actions by the interruption of the nerve pathways linking the thoracolumbar and sacral spinal cord centers to a supraspinal center controlling defecation.[11]

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