Gut dysfunction in patients with multiple sclerosis and the role of spinal cord involvement in the disease

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Objectives Bowel and bladder symptoms are highly prevalent in patients with multiple sclerosis (MS). Bladder dysfunction (affecting 75% of these patients) is caused by disease in the spinal cord, whilst the pathophysiology of bowel dysfunction is unknown. Pathways regulating both the organs lie in close proximity to the spinal cord, and coexistence of their dysfunction might be the result of a common pathophysiology. If so, the prevalence of bladder symptoms should be greater in patients with MS and bowel symptoms. This hypothesis is tested in the study. We also evaluated how patient-reported symptoms quantify bowel dysfunction.

Patients and methods The Neurogenic Bowel Dysfunction questionnaire and the presence of bladder symptoms were recorded in 71 patients with MS and bowel symptoms. Disability, a surrogate clinical measure of spinal cord disease, was assessed using the Expanded Disability Status Scale. Bowel and bladder symptoms were quantified by patient-reported frequency, expressed in time percentage (0, 25, 50, 75 or 100% of the time the symptom was perceived), and patient-reported severity on a visual analogue scale between 0 and 100.

Results The prevalence of bladder symptoms was 85%, which is higher than that expected in an unselected population of patients with MS. Neurogenic Bowel Dysfunction score was significantly correlated with both patient-reported frequency ($r=0.860$, $P<0.0001$) and severity of bowel symptoms ($r=0.659$, $P=<0.0001$), as well as with the Expanded Disability Status Scale ($r=0.526$, $P<0.0001$).

Conclusion Our findings suggest that gut dysfunction in patients with MS is secondary to spinal cord disease. Patient-reported bowel symptoms quantify bowel dysfunction well. *Eur J Gastroenterol Hepatol* 25:1044–1050 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Bowel symptoms (constipation and/or faecal incontinence) affect up to two-thirds of patients with multiple sclerosis (MS) [1], causing social isolation [2] and general reduction of quality of life [3,4]. Their origin is multifactorial and polypharmacy, disability, comorbidities and parity may have a causative role [5], but from the neurological standpoint MS can affect both extrinsic autonomic and voluntary control of the bowel. The effects on the end-organ include alterations of gut motility, anorectal sensation/coordination and anal sphincter control [6], but the neurological pathway that causes these disturbances is still unknown. This is mirrored in the lack of standards of treatment. MS symptoms relief, in the absence of a treatment for the primary neurological injury, is of paramount importance, but the area of bowel dysfunction remains the 'Cinderella' of MS research.

In contrast, bladder dysfunction, affecting around 75% of the patients with MS [7], has been well characterized. It is established that MS plaques in the spinal cord are central to cause urinary symptoms [8], and their treatment has been rationalized and standardized [9]. Neurological pathways regulating pelvic organs are in close proximity within the spinal cord; thus, it is unsurprising that bowel and bladder symptoms often coexist in patients with MS [1,10,11]. When this is the case, it could be that sclerotic plaques in the spinal cord simultaneously affect bladder and bowel function. However, in a study of MS patients with bladder dysfunction [12], the prevalence of bowel symptoms was only around 50%. This apparent discrepancy could be explained by the presence of the gut's enteric nervous system, which would allow preservation of some bowel function in the presence of

altered extrinsic hindgut modulation. This compensatory mechanism is not available to the bladder [13]. Therefore, we hypothesized that if bowel and bladder dysfunction can be caused by the same MS-related neurological alteration, in a selected population of patients with MS with bowel symptoms, a higher prevalence of bladder symptoms should be observed than that in the general MS population. The aim of the study was to test this hypothesis. We also analysed how well bowel dysfunction is assessed by patient-reported bowel symptoms, and any correlations between patient-reported bowel and bladder symptoms.

Anatomical considerations

The neural control of defecation is not clearly defined, but the centre concerned with it probably lies in the pons, and is under conscious cortical modulation [14]; defecation is also influenced by supraspinal centres [15].

It has been demonstrated that the spinal pathway for defecation, operating through sacral roots (S2–S4), lies in the lateral column of the cord, in close proximity to those pathways important for bladder control [15–17].

The neural pathways involved in physiological bladder control operate through complex bulbospinal–bulbar pathways, in close proximity to the lateral pyramidal tracts, and are mediated peripherally through the sacral roots S2–S4 [18,19]. Cortical voluntary control of micturition is established by connection of the frontal cortex to the micturition centre in the pons [20].

Types of multiple sclerosis

MS is characterized by an autoimmune response that results in the disruption of the myelin sheath in the central nervous system (demyelination), and the subsequent gliosis leads to the widespread occurrence of plaques in the white matter of the central nervous system that affects signal transmission. The natural history of the disease is of a progressive accumulation of neurological symptoms leading to severe disability. On the basis of the rapidity of progression and of accumulation of disability, MS is classified as relapsing remitting (most common, where symptoms appear and fade away), secondary progressive (usually follows relapsing remitting, characterized by a sustained build up of disability, independent of any relapses) and primary progressive (where the disease is progressive from the start).

Patients and methods

The Ethics Committee of University College of London granted Ethical approval (REC reference number: 08/h07164/7), and patients who participated in the study signed a consent form. Entry criteria included a definite diagnosis of MS and normal bowel function before the onset of MS. Exclusion criteria included: concomitant primary bowel pathology, comorbidities (i.e. diabetes,

thyroid dysfunction, coeliac disease, prostate hypertrophy, etc.) and sphincter injury. These were ruled out in all patients by means of negative investigation (colonoscopy, radiological or laboratory test) as appropriate. We recruited 71 consecutive patients with MS (55 women, aged 43 ± 9, median disease duration 78 ± 43 months) referred for bowel symptoms to a specialist neurogastroenterology clinic, in a tertiary referrals unit. None of the patients fulfilled any of the exclusion criteria.

Assessment of disability

Disability was measured with the Expanded Disability Status Scale (EDSS) [21], which is commonly used in patients with MS both in research and clinical practice. The EDSS scale ranges from 0 to 10 in 0.5 U increments that represent higher levels of disability and is principally based on ambulatory ability of the patient. For scores between 1 and 4.5 the patient is able to walk, and the score is mainly based on evaluation of eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual function, cerebral and mental function, and lastly any other system. With an EDSS above 5, mobility is impaired, at 7, the patient is wheelchair-bound and for scores above 8, the patient is bed-bound. Ten is death because of MS.

Disability is thought to be dependent on spinal cord involvement in MS, a common site of demyelinating lesions [22]. Although there is no correlation between the load of cord lesions on imaging and MS symptoms, it appears that spinal cord atrophy (signifying axonal loss) is a good radiological marker that correlates with MS symptoms [23,24]. Furthermore, EDSS correlates with spinal cord atrophy [23–25] and is a reflection of diffusion of spinal cord disease [26].

Symptoms assessments
Neurogenic Bowel Dysfunction questionnaire

No bowel symptoms questionnaire has been specifically validated in MS. Considering that constipation and faecal incontinence are often coexisting and alternating, we aimed to use an instrument that would evaluate both, as well as their impact on quality of life.

We therefore used the Neurogenic Bowel Dysfunction (NBD) questionnaire, which has been designed and validated in patients with spinal cord injury [27]. It includes questions about background parameters ($n = 8$), faecal incontinence ($n = 10$), constipation ($n = 10$), obstructed defecation ($n = 8$) and impact on quality of life ($n = 3$). The NBD score weights each symptom of bowel dysfunction in relation to its impact on quality of life, and scores are categorized as follows: 0 to 6 very minor dysfunction, 7 to 9 minor dysfunction, 10 to 13 moderate dysfunction and 14 to 47 severe dysfunction.

Patient-reported symptoms of bowel and bladder dysfunction

Patient-reported outcome measures are increasingly used in medical studies [28–30] and were assessed within a structured interview, conducted in the outpatient clinic. The alternating and fluctuating pattern of bowel habit in patients with MS is similar to that of irritable bowel syndrome. In patients with this condition, the product of frequency and severity of symptoms has been employed to quantify bowel function [31,32]. Therefore, each patient was asked what proportion of time of his or her life was affected by constipation and/or faecal incontinence, with five possible answers (0, 25, 50, 75 or 100% of the time). We then assessed severity by asking patients to use a visual analogue scale from 0 to 100, with 0 representing absence of symptoms, and 100 if the patient thought that bowel symptoms were the worst possible. These data were collected by a doctor experienced in assessing bowel symptoms (G.P.).

The presence of bladder symptoms and on-going treatment (antimuscarinic agents, use of intermittent self-catheterization, permanent catheter) was ascertained from the patient's history and clinical notes. Urgency was defined as a sudden compelling desire to pass urine that is difficult to defer [33]; urge urinary incontinence was defined as incontinence accompanied by or immediately preceded by urgency. The patient was also asked about difficulty of initiating bladder voiding (hesitancy), interruption of flow, sense of incomplete bladder emptying and use of pads.

We aimed to quantify bladder and bowel dysfunction uniformly. Therefore, we asked the proportion of time a patient perceived bladder symptoms affected his or her life, with five possible answers (0, 25, 50, 75 or 100% of the time). Severity was assessed on a visual analogue scale from 0 to 100, similarly to bowel symptoms. These data were collected by a doctor experienced in assessing bladder symptoms (J.P.).

Study design and statistical analysis

Scores from questionnaires and outcome of outpatient interviews were prospectively collected. Prevalence of bladder dysfunction was established as the presence of at least one urinary symptom at least 25% of the time. Data were either ordinal or not normally distributed (according to Kolmogorov–Smirnov test); thus, they are expressed as median and interquartile ranges and nonparametric tests were used. Age and disease duration are presented as mean and SD. Correlations between our parameters (EDSS, MS type and duration, NBD and patient-reported bowel and bladder symptoms) were evaluated using Spearman's rank test.

To evaluate how patient-reported symptoms quantified bowel dysfunction, we analysed correlations between NBD scores and patient-reported bowel symptoms with the Spearman's rank test (r = correlation coefficient). The values of the NBD score for each of the four different categories of patient-reported frequency of bowel symptoms (25, 50, 75 or 100%) were compared with the Kruskal–Wallis test.

Statistical significance was two-sided, and declared for P values of 0.05 or less. Statistical analysis was performed using the statistical software package IBM SPSS statistics v21 for Mac (IBM, Armonk, New York, USA).

Results

Patients' characteristics are reported in Table 1.

Of the interviewed patients, 85% had some degree of urinary symptoms.

Table 1 Patients' baseline characteristics

	All cohort ($n=71$, 55 female)	Primary progressive MS ($n=16$, 13 female)	Secondary progressive MS ($n=30$, 23 female)	Relapsing remitting MS ($n=25$, 19 female)
Age (years)	43±9	39±10	44±8	45±8
Disease duration (months)	78±43	58 (33.5–107.5)	84.5 (55–104)	67 (45–89)
EDSS	3 (1–4)	1.5 (0.5–3)	3.5 (1–4.5)	3.5 (1.75–4)
Neurogenic Bowel Dysfunction score	8 (6–13)	5.5 (4–8)	10.5 (6–14)	8 (7–18)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Table 2 Correlation analysis of bowel symptoms and patients characteristics

	Relapsing remitting MS (25)	Primary progressive MS (16)	Secondary progressive MS (20)	Disease duration (70, 47–100) (months)	EDSS (3, 1–4)
Neurogenic Bowel Dysfunction score	$r=0.168$ $P=0.161$	**$r=-0.355$** **$P=0.002$**	$r=0.137$ $P=0.253$	$r=0.125$ $P=0.297$	**$r=0.526$** **$P<0.0001$**
Bowel symptoms patient-reported frequency	$r=0.168$ $P=0.161$	**$r=-0.351$** **$P=0.003$**	$r=0.153$ $P=0.203$	$r=0.169$ $P=0.160$	**$r=0.645$** **$P<0.0001$**
Bowel symptoms patient-reported severity	$r=0.21$ $P=0.873$	$r=-0.120$ $P=0.318$	$r=0.81$ $P=0.500$	$r=0.79$ $P=0.512$	$r=0.112$ $P=0.352$

Data are reported as median and range.
Spearman's rank correlation coefficients (r) are given along with P value.
Statistically significant correlations are shown in bold.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Correlation analysis

Correlation of EDSS, MS type and duration, NBD and patient-reported bowel symptoms is summarized in Table 2. Figure 1 shows the graphical correlation between EDSS and NBD.

Correlation between bowel and bladder patient-reported symptoms is summarized in Table 3 and Fig. 2.

Evaluation of patient-reported symptoms

NBD scores were correlated with patient-reported frequency ($r = 0.860$, $P < 0.0001$) and severity ($r = 0.659$, $P < 0.0001$) of bowel symptoms.

There was significant difference between the values of NBD scores in the four categories of patient-reported frequency of bowel symptoms (Table 4 and Fig. 3).

Discussion

In our cohort, the prevalence of bladder dysfunction was 85%, which is higher than that expected in an unselected MS population, confirming our hypothesis and suggesting common pathophysiology of bowel and bladder dysfunction. Also, the NBD score was strongly correlated with the EDSS, which is a clinical indicator of spinal cord involvement in MS. These findings suggest that gut dysfunction in patients with MS is secondary to spinal cord involvement of the disease.

In patients with primary progressive disease, there was an inverse relationship with bowel symptoms (i.e. the higher the EDSS the lower the level of symptoms). The lower level of disability of this subgroup might explain this; however, it might just indicate that patients with other MS types have more bowel symptoms.

Fig. 1
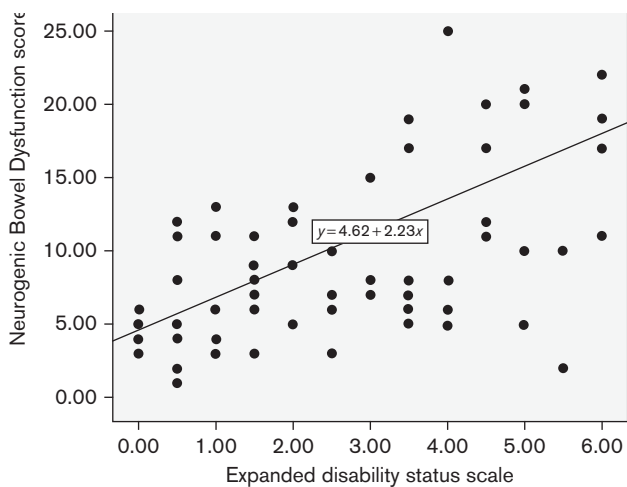
Correlation between Expanded Disability Status Scale and Neurogenic Bowel Dysfunction score (Spearman's rank test).

Fig. 2
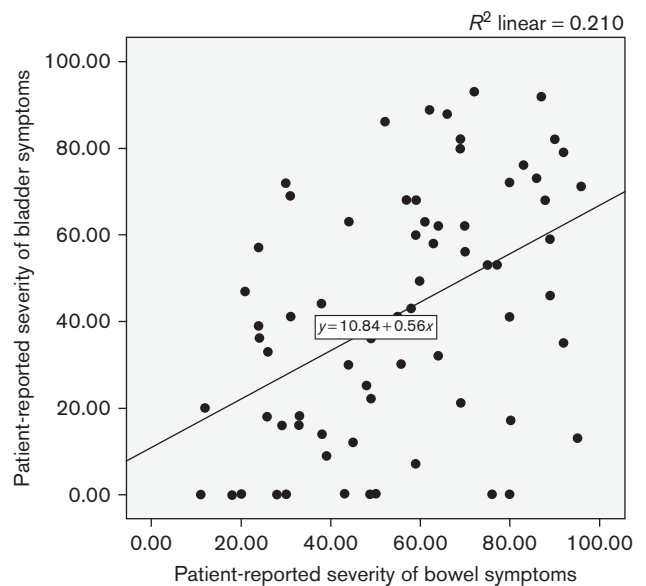
Correlation between patient-reported severity of bowel and bladder symptoms.

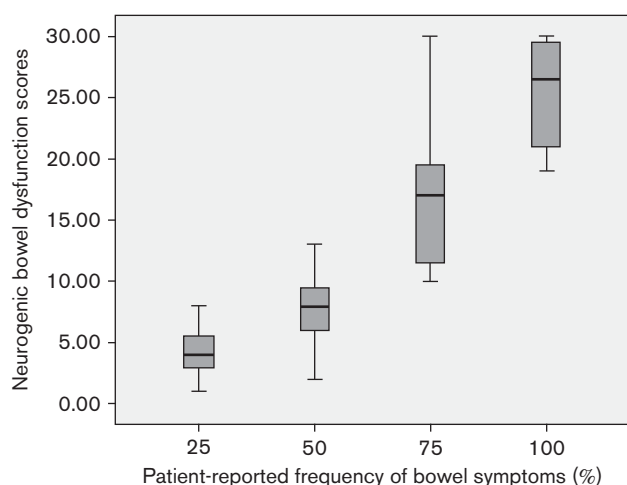**Table 3 Correlation analysis of bowel and bladder symptoms**

	Bladder symptoms	
Bowel symptoms	Patient-reported frequency (50%, 0–100%)	Patient-reported severity (41, 0–93)
Neurogenic Bowel Dysfunction score (8, 1–30)	$r = 0.342$ $P = 0.003$	$r = 0.659$ $P < 0.001$
Patient-reported frequency (50%, 25–100%)	$r = 0.367$ $P = 0.002$	$r = 0.300$ $P = 0.011$
Patient-reported severity (58, 96–11)	$r = 0.300$ $P = 0.011$	$r = 0.463$ $P < 0.0001$

Spearman's rank correlation coefficient and *P* values are given for correlation analysis of variable of bowel and urinary dysfunction.
All correlations were statistically significant.

Table 4 Comparison of Neurogenic Bowel Dysfunction scores between the four categories of patient-reported frequency of bowel symptoms

Bowel symptoms patient-reported frequency (%)	Neurogenic Bowel Dysfunction score	Kruskal–Wallis test
25	4 (3–5.5)	P<0.001
50	8 (6–9.5)	
75	17 (11–20)	
100	26.5 (21–29.5)	

Values of the Neurogenic Bowel Dysfunction scores for each group of bowel symptoms patient-reported frequency are shown.

Fig. 3

Comparison of Neurogenic Bowel Dysfunction scores between the four categories of patient-reported frequency of bowel symptoms. P value of Kruskal–Wallis test was less than 0.001 for all comparisons (Table 4).

Patient-reported frequency and severity of bowel and bladder symptoms were correlated.

With regards to bowel symptoms evaluation, simple questioning of patient-reported frequency and severity of bowel symptoms is as accurate as a validated questionnaire. Therefore, physicians, in the clinical setting, would be able to assess the impact of bowel dysfunction by determining the percent of time these symptoms are perceived. In contrast, the NBD score could be used to improve the quality of bowel studies in patients with MS.

The main strength of this study is the methodology used to evaluate our hypothesis, which is supported by anatomical considerations and supportive evidence. Also low level of disability in this cohort reduced the effect of confounders such as reduced mobility and polypharmacy.

There are also several limitations. A relevant one is the lack of a control group without bowel symptoms. Unfortunately, although bowel symptoms are so prevalent, it is very difficult to recruit such a reference population in a study.

It is well known that antimuscarinic drugs used for urological symptoms can cause constipation, and this could be a confounding factor affecting our findings. Still, in the study by Chia *et al*. [12], where patients were receiving pharmacological treatment for bladder dysfunction, no higher occurrence of bowel symptoms was observed.

Unfortunately we did not record drugs taken at the time. But antimuscarinics could have hypothetically masked symptoms of faecal incontinence, ultimately making patients overall more constipated. Still, patients with higher disability had high scores in both constipation and incontinence, suggesting that the confounder effect of drugs, if present, was minimal. In some of our male patients, the presence of undetected prostate hypertrophy might have also contributed to the presence of bladder symptoms.

Another limitation of this study is that bladder symptoms were not quantified with a standard questionnaire. The correlation of patient-reported bowel and bladder symptoms merits further evaluation, employing a validated urological questionnaire.

An element that merits further discussion is the low level of disability in our cohort. In fact for an EDSS of less than 5, functional systems other than the spinal cord are relevant. Overall, our findings suggest that, although the cause of bowel dysfunction in patients with MS is multifactorial, the spinal cord plays a central role from the neuropathophysiology standpoint. Reflex activity in the spinal cord has a crucial role in regulating bowel function, and this has been widely demonstrated in patients with spinal cord injury [34–36], with whom MS patients share many similarities. Physiological studies in MS showed that the conduction in the central motor pathways to the sphincteric sacral neurons is delayed [37]. In addition, somatosensory evoked potentials from the spinal cord to the brain have been shown to be delayed in MS compared with controls, with normal potentials recorded at the lumbar spine [38].

The loss of cortical modulation of spinal reflex activity can result in autonomic dysfunction of colonic motility, resulting in a prevalence of the sympathetic tone and slow colonic transit (constipation) [38], or in the loss of inhibition of parasympathetic output, uncontrolled colonic contractions and diarrhoea [39]. This could be the result of unopposed parasympathetic stimulation of the vagus nerve that supplies the colon up to the splenic flexure.

In addition to the motor effects, anorectal hyposensitivity is another common feature of MS and spinal cord injuries that can affect the anorectum [1].

Disability measured with EDSS (reflective of the spinal cord involvement in MS) has been found consistently, as

in our study, to correlate with bowel symptoms [10,11]. It could be that there is a specific pattern of neurological deficit resulting in lower limb dysfunction and bowel symptomatology, and/or that difficulty accessing the toilet contributes to bowel symptoms.

A parallel phenomenon to bowel and bladder dysfunction, secondary to spinal cord disease, could be pelvic floor incoordination. In fact, the loss of cortical modulation of spinal reflexes due to MS plaques may result in autonomous functioning of the bladder, explaining bladder detrusor dyssynergia [40]. This is the uncoordinated contraction of the detrusor muscle when the bladder attempts voiding. A similar and parallel mechanism might result in pelvic floor dyssynergia (uncoordinated contraction of the puborectalis and abdominal muscles on voiding the rectum), causing obstructed defecation and incomplete rectal emptying [41,42]. A full rectum might in turn precipitate urgency and faecal incontinence in the presence of anal sphincter weakness and anorectal hyposensitivity or rectoanal incoordination [43], explaining coexistence of constipation and faecal incontinence in patients with MS. Pelvic floor dyssynergia might be also behavioural, and reversible with biofeedback [44]. Successful biofeedback in non-neurological patients is associated with gut-specific changes in autonomic outflow to the large bowel, with spinal efferents playing a key role [45]. Therefore, improvement of bowel symptoms with biofeedback might be attributed to the ability to recruit alternative neurological pathways through residual spinal cord function. This also suggests that neuromodulation in patients with residual spinal cord function could represent a targeted treatment option.

To improve our understanding of the natural history and aetiology of bowel dysfunction in MS, it would be helpful to correlate imaging and physiological studies in MS patients with bowel symptoms. Stratification of patients according to spinal cord disease, as clinically measured by the EDSS, could aid in the stratification of patients for targeted treatment.

Conclusion
Our findings and available evidence suggest that spinal cord involvement in MS is central to determination of bowel symptoms. This is highly relevant both to improve our understanding of bowel dysfunction in MS and in the development of further studies on the subject that should stratify patients on the basis of the clinical extent of spinal cord disease (EDSS). Physicians can easily assess lower limb function (a major determinant of EDSS), and a pragmatic treatment algorithm based on this parameter could be employed to improve bowel care in MS patients in the community. Residual spinal cord function could be a target of treatments such as neuromodulation, physiotherapy or biofeedback. The knowledge generated by studies on MS-related bowel dysfunction can also improve

our understanding of the neural control of defecation and treatment of functional bowel disorders.

Finally, patient-reported frequency of bowel symptoms evaluates bowel dysfunction well, and so it is a valuable tool in the clinical setting. Equally, the Neurogenic Bowel Dysfunction score could be used to improve the quality of bowel studies in patients with MS.

Conflicts of interest
There are no conflicts of interest.

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