

Gastric motility dysfunction in patients with multiple sclerosis assessed by gastric emptying scintigraphy

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BACKGROUND: Gastrointestinal tract symptoms are common in patients with multiple sclerosis (MS), especially constipation and/or fecal incontinence.

AIMS: To assess gastric emptying in patients with MS to detect the severity of autonomic disturbances in the gastrointestinal tract, and to find the relationship between lower bowel disturbances and the rate of gastric emptying.

METHODS: Forty-nine patients with definite MS and 20 control subjects were included in the study. All patients underwent full neurological examination and magnetic resonance imaging of the brain and spinal cord. The labelled meal for gastric emptying scintigraphy consisted of cooked eggs mixed with 3 mCi of technetium-99m colloid, and was followed by serial images at 15 min intervals for 2 h.

RESULTS: Five studies were excluded due to technical artifacts. Twenty-one patients (47.7%) demonstrated slow emptying, 15 (34.1%) demonstrated normal and eight (18.2%) demonstrated fast clearance curves. The mean half-time of gastric emptying in MS patients was 96.6±22.4 min and the controls showed a mean half-time of 41.3±18.7 min ($P<0.05$).

The half-time was longer in patients with constipation; nevertheless, it showed no significant difference compared with patients without constipation ($P=0.197$). Moreover, although half-time was shorter in patients with fecal incontinence, there was not a significant difference compared with those without fecal incontinence ($P=0.654$).

CONCLUSIONS: The gastric emptying rate is slow in MS patients. As for lower bowel disturbances, the gastric emptying rate was obviously affected in patients complaining of constipation and fecal incontinence, although statistical significance was not reached.

Key Words: *Gastric emptying scintigraphy; Gastrointestinal tract autonomic disturbances; Multiple sclerosis*

The autonomic nervous system innervates every organ in the body and is actively involved in the function of these organs (1). Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). MS is the most common disabling neurological disorder affecting people between 20 and 45 years of age. Current prevalence rates for MS are 1/1000 in the United States and 2/1000 in Europe. MS affects women more commonly than men, with a ratio of 2:1 (2-5).

MS involves myelinated white matter pathways in the brain and spinal cord and is caused by an autoimmune attack of CNS

Une dysfonction de la motilité gastrique chez les patients atteints de sclérose en plaques, évaluée au moyen d'une scintigraphie de la vidange gastrique

HISTORIQUE : Les symptômes intestinaux sont courants chez les personnes atteintes de sclérose en plaques (SP), notamment la constipation et l'incontinence fécale.

OBJECTIFS : Évaluer la vidange gastrique chez les patients atteints de SP afin de déceler la gravité des troubles du système nerveux autonome dans le tube digestif et trouver le lien entre les perturbations intestinales basses et le rythme de vidange gastrique.

MÉTHODOLOGIE : Quarante-neuf patients atteints de SP définie et 20 sujets témoins ont participé à l'étude. Tous les patients ont subi un examen neurologique complet et un examen d'imagerie par résonance magnétique du cerveau et de la moelle épinière. Le repas marqué pour la scintigraphie de la vidange gastrique était constitué d'œufs cuits mélangés à 3 mCi de colloïde de technétium 99 m et suivi d'images sérielles à intervalles de 15 minutes pendant deux heures.

RÉSULTATS : Cinq études ont été exclues en raison d'artéfacts techniques. Vingt et un patients (47,7 %) ont démontré une vidange lente, 15 (34,1 %), une vidange normale, et huit (18,2 %), des courbes de clairance rapide. La demi-vie moyenne de la vidange gastrique des patients atteints de SP était de 96,6±22,4 min, tandis que celle des sujets témoins était de 41,3±18,7 min ($P<0,05$).

La demi-vie était plus longue chez les patients constipés, sans pour autant afficher une différence significative par rapport aux patients non constipés ($P=0,197$). Par ailleurs, même si elle était plus courte chez les patients atteints d'incontinence fécale, on n'a remarqué aucune différence significative par rapport aux patients sans incontinence fécale ($P=0,654$).

CONCLUSIONS : Le rythme de vidange gastrique est lent chez les personnes atteintes de SP. Dans le cas de perturbations intestinales basses, il était de toute évidence touché chez les patients souffrant de constipation ou d'incontinence fécale, bien qu'on n'ait obtenu aucune signification statistique.

myelin leading to loss of saltatory conduction and conduction velocity in axonal pathways. It is characterized by periventricular demyelination with preservation of axons. MS is a chronic demyelinating disease characterized by disseminated, multifocal lesions that lead to extensive multiple clinical features related to the involvement of the autonomic nervous system (1,6).

The autonomic dysfunction encountered in MS includes impairment of cardiovascular autonomic reflexes leading to hypotension and urinary tract and sexual dysfunctions, which are present in the majority of patients with MS (5,7,8).

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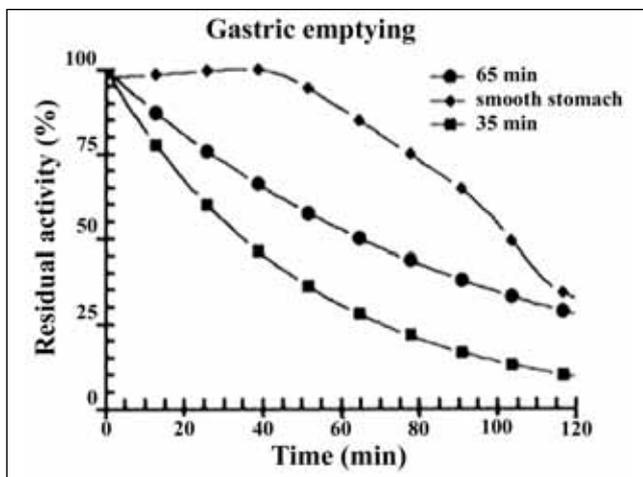


Figure 1) Gastric emptying scintigraphy illustrating the obvious delay in gastric emptying as denoted from the slope of the curve and the prolonged half-time (half-time = 68 min)

The gastrointestinal tract (GIT) constitutes one of the largest organs whose motor, transport, secretory, storage and excretion functions are controlled by the autonomic nervous system (9). Control of gastrointestinal motility involves an integrated chain of neural centres present along the walls of the digestive system, prevertebral sympathetic ganglia, spinal cord and the brain (10).

Gastrointestinal symptoms, especially constipation and/or fecal incontinence, are common in patients with MS. However, GIT symptoms are often overlooked in MS (11).

The aim of the present study was to assess gastric emptying in patients with MS, to detect the severity of autonomic disturbances in the gastrointestinal tract. The second goal was to find the relationship between lower bowel disturbances and the rate of gastric emptying from the stomach.

METHODS

Patients

The present study was conducted on 49 patients with definite MS, according to criteria proposed by Poser et al (12). Twenty healthy control subjects, who were age- and sex-matched with the patient group, were included. Patients were recruited in the period from March 2001 to April 2003 from the inpatient ward of the Neurology Department, Cairo University Hospital. Patients with relapsing remitting (RR-MS), secondary progressive (SP-MS), and primary progressive (PP-MS) types were included. RR-MS was defined as episodes of acute worsening of neurological function followed by a variable degree of recovery. SP-MS was defined as initial RR disease course followed by progression with or without occasional relapses, minor remissions and plateaus, and PP-MS was defined as disease progression from onset with occasional plateaus and minor improvements (13). Most patients were in acute relapse or showed disease progression by clinical evidence. Patients with possible causes of dysautonomia, such as those with endocrinal disorders such as diabetes mellitus, were excluded. Other causes for exclusion were collagen vascular diseases and a history of drug intake that might affect autonomic function (eg, anticholinergic medications or narcotic analgesics). All patients included in the study were subjected to full clinical evaluation and

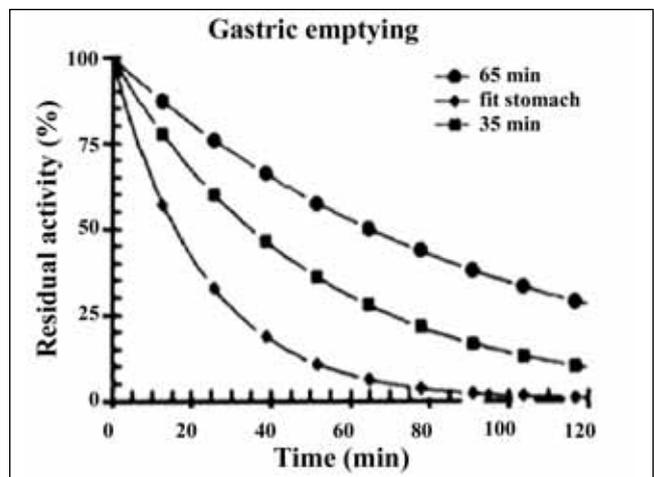


Figure 2) Gastric emptying scintigraphy showing rapid rate of gastric emptying with half-time of only 16 min. This patient was complaining of fecal incontinence

full neurological examination. Assessment of the clinical disability was performed using the Kurtzke Multiple Sclerosis Rating Scales, the Expanded Disability Status Scale and the Functional Systems Scale (14). Radiological assessment was carried out by magnetic resonance imaging (MRI) of the brain and the spinal cord (cervical and dorsal areas). Verification of the site of plaques was interpreted thoroughly by a specialized neuroradiologist to be correlated with autonomic dysfunction.

Radionuclide gastric emptying (scintigraphy)

Radiopharmaceuticals and equipment: All patients were prepared by fasting for a period of 4 h to 6 h before the gastric emptying study. Three mCi (111 MBq) of technetium-99m colloid were mixed with two scrambled eggs and cooked. The labelled meal consisted of the cooked eggs placed inside bread slices (in sandwich form) and was eaten with one glass of water (200 mL). The imaging was performed using a large field of view gamma camera with dual detectors (Adac, Vertex, USA). The gamma camera was equipped with an all-purpose parallel holes collimator. The energy window was 20% centred at 140 KeV.

Imaging protocol

The two camera heads were located anteriorly and posteriorly to the whole abdominal area to get the best view. Serial static digital images (64×64) at 15 min intervals were acquired immediately after the patient finished ingesting the scrambled eggs meal. Acquisition of images continued for a total time of 2 h.

Processing of the images and display: A region of interest was drawn around the entire stomach in both the anterior and posterior projections. The small intestine was excluded from these regions of interest as much as possible in each image. The counts in each image were corrected for decay. The results were plotted in a time-activity curve format with 'time' on the x-axis and decay-corrected 'gastric counts' on the y-axis (Figures 1 and 2). The best linear fit to the data was estimated, and the gastric emptying half-time from the fitted data was calculated by drawing a horizontal line through the y-axis at a point corresponding to half the maximum (initial) counts. Then half-time was calculated from the x-axis at the point where it was crossed by the drawn line. The normal values for the

TABLE 1
Demographic data for the subjects included in the study

Variable	Controls	Patients	P
Age range (years)	18 to 48	19 to 50	0.754
Mean age (years)	32±8.6	33.5±7.65	0.754
Males	10	19	0.3
Females	10	30	0.3
Total	20	49	

half-time in the nuclear medicine laboratory at Cairo University Hospital are in the range of 55 min to 85 min.

Interpretation of the results

There is some variation in the shape of the time-activity curve for the clearance of gastric contents from the standard model of lag and linear emptying phases, because the study was not acquired in a continuous dynamic mode. Therefore, the linear disappearance slope describes the emptying rate. In addition, visual inspection of the serial static images and the calculated half-time with qualitative description was performed. A semiquantitative score based on visual analysis for the disappearance slope of the gastric emptying curve was implemented in the current work. The scoring system was a 5-point scale where 1 = definite slow descent in the disappearance slope (almost plateau), 2 = slow descent in the disappearance slope, 3 = normal descent in the disappearance slope (linear descent), 4 = fast descent in the disappearance slope and 5 = definite fast descent in the disappearance slope (very steep).

Statistical analysis

Data management and statistical analysis were performed using the Statistical Analysis System (SAS Institute Inc, USA). Numerical values were summarized as mean ± SD or frequency when appropriate. Categorical variables were presented as percentages. Differences among different subgroups in the study were evaluated by the Mann-Whitney nonparametric significance test, which is suitable for small sample sizes and is equivalent to Student's *t* test.

RESULTS

The study included 49 patients and 20 normal control subjects. The patients included 30 females and 19 males, with age ranging from 19 to 50 years, with a mean age of 33.5±7.65 years. The controls included 10 males and 10 females. The age of the control subjects ranged from 18 to 48 years, with a mean age of 32±8.6 years. No statistically significant difference existed between the two groups regarding age or sex ($P=0.754$ and $P=0.30$, respectively) (Table 1). The clinical types of MS included in the study were 32 patients (65.5%) with RR-MS, 10 (20%) with SP-MS and seven (14.5%) with PP-MS.

Autonomic dysfunction in the form of gastrointestinal symptoms was present in all patients. By clinical history and carefully analyzed GIT symptoms, the patients were categorized as having constipation when they had passage of excessive dry, small or infrequent stools less often than every other day and less than 50 g a day provided that they had adequate dietary intake. The fecal incontinence group included those patients who had lack of sphincteric control over the act of defecation, provided there was no diarrhea or loose stools. In the current study, of the 49 patients with MS, 28 patients (57%) complained of constipation, 18 (36.7%) suffered from

TABLE 2
Frequency of different brain sites and spinal cord plaques on magnetic resonance imaging in multiple sclerosis patients

Site of plaques	n=49	%
Periventricular	41	83.67
Brainstem	28	57.14
Centrum semiovale	17	34.7
Corpus callosum	13	26.3
Cerebellum	11	22.4
Spinal cord plaques	n=42	%
Positive	35	84.4

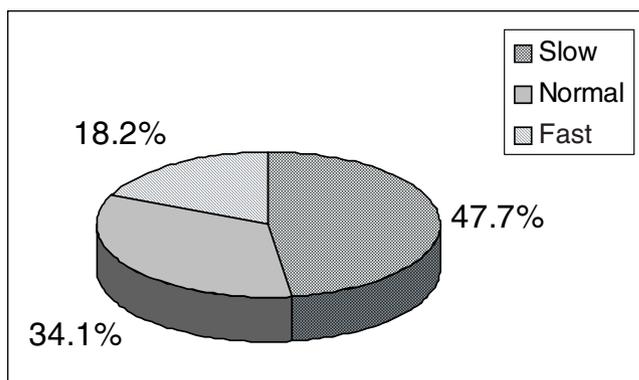


Figure 3) Distribution of different patterns of gastric emptying rate in the patients with multiple sclerosis

fecal incontinence more than once during the course of the disease, and three patients (6.3%) gave symptoms of dyspepsia not related to steroid therapy. The total number and the percentage of distribution of MS plaques in MRI results of the brain and spinal cord imaging are presented in Table 2. The highest numbers of plaques were present in the periventricular region, brain stem and spinal cord regions.

Gastric emptying by scintigraphy

Five studies of gastric emptying scintigraphy were excluded due to technical artifacts in three studies and vomiting in two patients. The remaining 44 patients were included in the analysis. Twenty-one patients (47.7%) showed slow emptying curves (grades 1 and 2) as illustrated in Figure 3; 15 (34.1%) showed normal curves (grade 3), and eight (18.2%) showed fast clearance curves (grades 4 and 5) (Figure 2). The mean half-time of gastric emptying in patients was 96.6±22.4 min and the controls showed a mean of 41.3±18.7 min, with a significant statistical difference between the two groups ($P<0.05$) (Figure 4).

Gastric emptying half-time and GIT symptoms

The mean half-time was greater in patients with constipation (64.4±23.2 min); nevertheless, there was no statistically significant difference between patients with constipation and patients without constipation ($P=0.197$). Moreover, although the mean half-time was lower in patients with fecal incontinence (49.9±16.8 min), there was no statistically significant difference when compared with those without fecal incontinence ($P=0.654$) (Table 3).

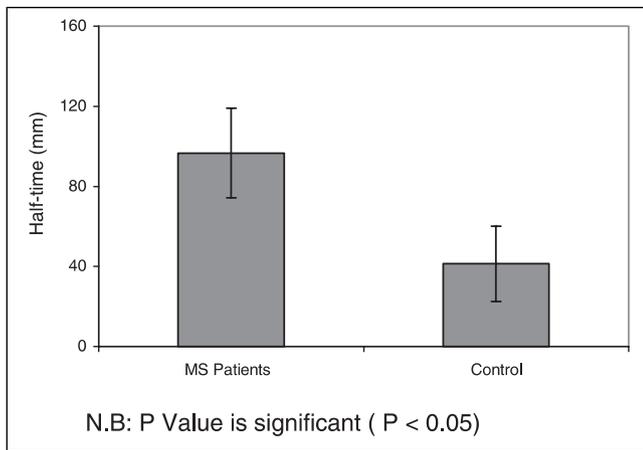


Figure 4) Comparison between the mean value for the half-time of gastric emptying in patients with multiple sclerosis (MS) and the normal control group

Gastric emptying half-time and MRI findings

Separate analysis for the half-time values according to the site of plaques in the MRI was carried out. There was no significant difference in the mean half-time between different patient subgroups with periventricular, centrum semiovale, corpus callosum, cerebellar, brainstem or spinal cord plaques ($P>0.05$ for all).

DISCUSSION

Autonomic dysfunction is frequently observed in patients with MS, but clinical studies have shown contradictory findings regarding the frequency and type of abnormalities in autonomic function tests (1).

In the present study, the gastric emptying rate was prolonged in MS patients compared with controls, as evidenced by the longer mean half-time in the former ($P<0.05$). This was consistent with the reports that document gastric dysfunction in patients with MS who presented with symptoms of delayed gastric emptying. The complaints reported were mainly a sense of fullness, nausea and persistent vomiting, recurrent hiccups and gastroesophageal reflux (15,16).

Prevalence of lower bowel dysfunction

The prevalence of lower bowel dysfunction in patients with MS is much higher and has been reported to range from 41% to 68% in different studies (17-20).

In the present study, the symptoms of bowel dysfunction encountered were mainly constipation, in approximately 59% of patients, and fecal incontinence, either alone or in association with constipation, in approximately 36%. Many studies are in agreement with these findings. Sullivan and Ebers (21) reported that 53% of their patients with MS had constipation, and Minderhoud et al (22) reported that 52.7% of MS patients complained of irregularities in their defecation pattern. Another study (18) of 77 patients with MS found that 52% had bowel dysfunction. Among a group of 209 patients with MS, 41.3% reported bowel dysfunction (19). Hennessey et al (11) reported that 54% of 221 patients with MS were constipated and 29% suffered from fecal incontinence.

In the current work, although the main symptoms of GIT automatic dysfunction were related to the large bowel, the method used to assess GIT motility was ‘gastric emptying’ because of its availability and because it is relatively simple to

TABLE 3
Half-time (T1/2) rate of gastric emptying in the subgroups of multiple sclerosis (MS) patients included in the present work

Variable	T1/2 (mean ± SD)	P
MS patients	96.6±22.4	<0.05
Controls	41.3±18.7	<0.05
MS patients with constipation	64.4±23.2	0.197
MS patients without constipation	51.4±20.2	0.197
MS patients with fecal incontinence	49.9±16.8	0.654
MS patients without fecal incontinence	69.4±34.8	0.654

perform. In addition, the use of gastric emptying scintigraphy was supported by literature data stating that gastric emptying may be altered by small bowel or colonic dysfunction and that chronic intestinal dysmotility is associated with prolonged gastric emptying (23,24). Moreover, experimental rectal distension or constipation can impair gastric emptying and upper GIT motility (25).

Gastric emptying in lower bowel dysfunction

Our results showed that the mean half-time was longer in patients with constipation, implying a slower rate of gastric emptying. On the other hand, the mean half-time was shorter in patients with fecal incontinence, indicating a faster rate of gastric emptying. Nevertheless, these differences in the rate of gastric emptying between patients with constipation or fecal incontinence and patients without constipation or fecal incontinence was not statistically significant ($P=0.197$ and $P=0.654$, respectively).

This agrees with the findings of Chatterton (26), who stated that there is often a poor correlation between lower bowel symptoms and the degree of gastric emptying.

This explanation for this poor correlation is partly related to the fact that the causes for lower bowel disorders are not fully understood. A number of possible pathophysiological mechanisms, rather than a single neurological deficit, are thought to result in these constipation and incontinence symptoms (20).

Constipation in MS can result from the absence of normal increment in colonic motility after eating (27,28). Chia et al (29) found that paradoxical puborectalis contraction is present in MS patients and can lead to constipation. Other nonneurological factors that contribute to constipation are lack of exercise arising from immobility, inadequate dietary fibre and hydration, and the effects of certain medications such as anticholinergics used to control irritative bladder symptoms and tricyclic antidepressants (20,30).

The pathophysiological causes for fecal incontinence in MS patients are related to poor voluntary squeeze pressure (28), abnormal rectal sensation (31) and obstetric injury causing weakness of the anal sphincter (a peculiar contributing factor in multiparous women with MS) (32).

Gastric emptying and the severity of MS

No statistically significant correlation was detected between gastric emptying abnormalities and the Expanded Disability Status Scale score in the current study. In agreement with our results, Minderhoud et al (22) and Chia et al (29) found that severe constipation could occur in patients with little general neurological disability due to MS. There was no statistically

significant correlation between gastric emptying abnormalities and the duration of the disease or the number of attacks. Also, no difference existed between males and females or among the different types of MS. In agreement with this, Minderhoud et al (22) found that bowel disturbances have no correlation to the age, sex and disease duration in MS patients.

There was no particular association between the mean half-time and the MRI findings, which agrees with the findings of Hawker and Frohman (30) that bowel disturbances were not due to a specific neurological lesion in the CNS but were instead due to the reasons mentioned previously.

CONCLUSIONS

Autonomic function impairment is common in MS patients and GIT autonomic disturbances are frequently encountered. The gastric emptying rate was clearly slower in MS patients than in the controls. As for lower bowel disturbances, although statistical significance was not found, the gastric emptying rate was obviously affected in patients complaining of constipation and fecal incontinence.

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