Neurogenic Bowel Dysfunction in subjects with Brain Injury: Prevalence, Risk Factors, Clinical Characterization and Physiopathology.

Jenny Rosario Haya Hidalgo

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DIRECTOR DE LA TESI:

Dra. Silvia Delgado Aros

DEPARTMENT OF EXPERIMENTAL AND HEATLH SCIENCES

Dedication

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ABSTRACT

To date, there are scarce data on bowel dysfunction (BD) in patients after brain injury (BI). Until now, only fecal incontinence (FI) has received attention and it has been mainly associated to patients' age or performance status after the brain damage. In this thesis we report on the elevated incidence of BD in patients after an acute BI event, including FI but also diarrhea, severe constipation, abdominal pain and distention. We have characterized the clinical manifestations of these gut dysfunctions and measured their impact on QOL. We have also explored risks factors and underlying pathophysiologic mechanisms. We conclude that BD is very common and long-lasting in patients who experiment acute BI, it may have a major impact on QOL and it appears to depend on damaged brain area. The physiologic studies suggest bowel dysfunctions have a distinct etiopathogenesis compared to patients with the same clinical manifestations but no brain injury.

RESUM

Hi ha poques dades sobre disfunció intestinal (DI) en pacients que han patit lesió cerebral (LC). La incontinència fecal (IF) és la única que ha rebut atenció i s'ha considerat associada a edat i l'estatus funcional després de la LC. En aquesta tesi comuniquem la elevada incidència de DI en aquests pacients, incloent-hi la IF però també el restrenyiment sever, el dolor i la distensió abdominals. Hem caracteritzat les manifestacions clíniques d'aquestes DI i hem mesurat el seu impacte en la qualitat de vida. Hem explorat també factors de risc i mecanismes fisiopatològics subjacents. Concloem que la DI és molt comú i perdura en pacients amb LC. Pot tenir un gran impacte en la qualitat de vida i sembla que depèn de la zona cerebral afectada. Els estudis fisiològics realitzats suggereixen que les disfuncions intestinals tenen una etiopatogènesi diferent a la dels pacients amb similars manifestacions però sense lesió cerebral.

GENERAL INTRODUCTION

Bowel Dysfunction in Patients with Brain Injury

Bowel dysfunction (BD) or neurogenic bowel as is used generally in the neurology field refers to clinical manifestations that include fecal incontinence, impaired spontaneous rectal evacuation, and slow colonic transit or colonic inertia (1).

Data from studies in patients with sacral cord injury show that BD is a highly prevalent problem and rated by patients as one of their worst sequels (1)(2)(3)(4). However, there are scarce data on BD after brain injury (BI). Only the occurrence of fecal incontinence (FI) right or shortly after BI has received some attention and it has been deemed mainly due to the impact of brain damage on patient mobility and cognitive functions (5)(6)(7). However, data on this issue are scarce and other precipitating factors of FI, such as the presence of diarrhea or liquid stools have not been taken into account before. Moreover, predictive factors of post-BI development of other BD such as constipation or abdominal pain or distensiom have not been previously evaluated. The incidence figures and impact on quality of life of these gut dysfunctions in BI patients are also unknown.

Gut sensory and motor functions are controlled by the enteric nervous (ENS) and central nervous systems (CNS), which share information continuously through the extrinsic innervation (Brain-Gut axis)(8) (9) **(Figure 1)**. Visceral information is transmitted proximally along spinal and vagal afferents projecting to the CNS where this information is integrated to activate extrinsic visceral efferents that will enable adequate gut motor and secretory responses(8)(10)(11) Conscious perception of physiologic gut sensations, such as desire to defecate, is also necessary for an adequate control of some of its main functions, primarily defecation and continence, and this relays as well on a healthy brain-gut axis. When the rectum is filled with gas and feces, the ENS responds inducing a contraction of the rectum wall muscle and a relaxation of the internal anal sphincter distal to the fecal bolus, to prepare for a physiologic evacuation. In case of a functional brain-gut axis, rectum filling is consciously perceived and hence, we can voluntarily squeeze or relax the external anal sphincter and elevator ani, depending on our judgment and social context, through activation of the pudendal nerve, a somatic nerve under conscious control (12) (13)(14)(15)(16).

In patients with BI, hampered central integration and processing of visceral information transmitted through visceral afferents might conceivably alter efferent signals that are sent back to the gut and therefore cause bowel malfunction. For instance, altered neural control of gut wall basal tone could ultimately facilitate abdominal distention. Dysfunctional central regulation of visceral afferent signals such as gastric or colonic distension due to the presence of an alimentary bolus or feces, respectively, might induce altered peristaltic response and thus, altered gastric emptying, slow transit constipation or hampered rectal evaquation. Altered integration of visceral sensory signals might also facilitate increased perception of physiological gut events leading, for example, to chronic abdominal pain or, on the contrary, decreased perception of these events. For instance, if rectal filling is not adequately perceived, the immediate reflex response that leads to external anal sphincter squeeze might be hampered, which would facilitate development of FI.

Evaluation of Gastrointestinal Motor and Sensory Functions

There are several techniques that allow assessment of the motor and sensory functions of the GI tract. We have used state-of-the art and validated techniques such as the wireless motility capsule (WMC) that allow the measurement of whole-gut transit and motility and allows to differentiate which parts are affected. To assess ano-rectal function in patients with FI and constipation syndromes we have used high resolution anorectal manometry.

Wireless motility capsule (WMC)

The WMC system comprises of an indigestible single-use capsule, an external data receiver and display/analysis software **(Figure 2)**. The capsule has dimensions of 26.8 mm 11.7 mm, similar to the wireless endoscopy capsule (WCE; PillCam; Given Imaging, Israel) and is capable of measuring temperature (range 25–49○C), pH (range 0.05–9.0) and pressure (range 0–350 mmHg).

The WMC contains a battery that lasts at least for 5 days (17) and a high-frequency transmitter that sends data to an external receiver. Through combining the interpretation of pH, time, pressure, and temperature data, the WMC allows differentiated measurement of gastric, small bowel and colonic transit.(18) (19)(20)

In addition to transit times, the WMC also measures GI intraluminal pressures, recording both the amplitude and frequency of contractions.

Comparison of wireless motility capsule to other techniques

As mentioned, there are other techniques available for the measurement of GI transit times.

- Regarding the stomach

Gastric Scintigraphy is currently considered the gold standard for measurement of gastric emptying(21).However, it involves the patient consuming a ^{99m} technetium-labelled meal and at least 4hours of patient-hospital measurements with a gammacamera. Head to head analyses between gastric scintigraphy and the wireless motility capsule show that the latter estimates concordate well with those obtained with the gold standard and allow correct discrimination between health and disease.(18)

There exist other alternatives that provide indirect estimates of gastric emptying such as the 13C isotope breath test; however, this technique involves radiation and requires also that the patient stays in the hospital for at least 6 hours.

On the other hand, there are other techniques that allow evaluation of gastric motor activity such as the gastric barostat or the manometry. These techniques involve intubation of the patient and require the patient to stay in the hospital during the recordings.

- Regarding the small bowel

There are a number of methods that are presently utilized to evaluate small bowel motility or small bowel transit time (SBTT) which include antroduodenal manometry (ADM), breath testing, a small bowel radio- graphic series, and whole-gut scintigraphy (WGS). However, as seen with the stomach, many of these methods are invasive, involve radiation, may need the patient to remain in the hospital for several hours and many lack of standardization.

Regarding the validity of pressure data obtained by the WMC, several studies performed in subjects that underwent concurrent ADM and WMC have shown a good concordance with high- amplitude phasic contractions before exit of the capsule into the small bowel as recorded with the WMC with the phase <III of MMC recorded by the ADM. These studies have also shown a very good correlation of gastric emptying time measured by

the WMC and the time at which the first phase-III MMC is re-established following feeding. (22) (23)**.**In the latter study WMC detected 86% of MMC events measured by ADM with a negative predictive value of 99.9%.

- Regarding the colon

There are also alternatives to measure colonic transit. The methods that has been widely accepted and used in scientific studies evaluating GI transit is scintigraphy. As explained with gastric scintigraphy this technique involves radiation, a significant cost in equipment and well trained personnel and requires the patient to come to the hospital nuclear medicine facilities several times.(24).

Another available and validated method to measure colonic transit time the one that uses radiopaque markers (ROM). There is 80% agreement to diagnose delayed colonic transit between ROM and WMC. However, this technique involves radiation as well and requires the patient to present to the hospital to perform abdominal x-rays on one or two occasions after the initial visit.(25)(26) **.**

Colonic motor activity can also be measured using manometry and barostat. As with the antroduodenal manometry, this technique, whether combined or not with barostat, requires colonic cleansing and intubation plus long-periods of recording. It has also high costs in well trained personnel and is not available in most centers.

- Whole-gut transit time

This can be also measured using scintigraphy. Simultaneous measurements of whole gut transit have been made by scintigraphy and the WMC and showed good correlation between the two methods to evaluate whole gut transit time (19).

Therefore, we chose for these thesis aim of measuring GI motor activity to use the less invasive and more efficient technique that was available. Thus, we chose WMC since it would allow in only one non-invasive test to measure whole gut transit times as well as to obtain further information on stomach and small bowel motility, a physiologic function that has never been tested in BI patients before and compare it with a control population with similar clinical complaint but void of any neurological derangement.

High Resolution Anorectal Manometry

Impaired colonic emptying might be explained by different underlying disorders. The neuro-muscular apparatus of the colon may be affected and thus, peristalsis will be suboptimal or even absent. This might affect the colon from the ascending colon to the rectum, or only affect segments of the large bowel. In the general population impaired colonic emptying is also present even in the absence of altered colonic neuro-muscular system and might be due to altered coordination during rectal expulsion of feces.

Currently, it is believed that any constipation that might appear in patients with BI is probably related to a lack of adequate hydration and fiber intake as well as lack of mobility. These would not differentiate them from the general population who does not suffer from brain injury and report constipation.

However, our hypothesis is that damage to special brain areas might affect neuro-muscular control both of the colon and the anorectal apparatus involved during defecation. Increased anal resting tone or failure to relax the puborectalis are two of the potential mechanisms underlying altered rectal evacuation. .As well as inadequate strength of patients who may not be able to generate the necessary rectal forces to expel stools during evaquation. Thus, to evaluate these functions and compare them to a general population sample with constipation we included high resolution anorectal manometry in our studies.

Therefore, in this thesis we aimed to evaluate, in patients that have experienced acute BI and recover without significant impact on their performance-status:

1. Study-The incidence and risk factors of long-term clinically significant BD, characterize the different clinical syndromes and measure their impact on QoL.

2. Motility and transit times of the stomach, small bowell and the colon as well as anorectal motor and sensory function in patients from the 1st study with BD compared to patients with BD without BI.

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STUDY 1. PREVALENCE, CLINICAL CHARACTERIZATION AND PREDICTION FACTORS OF LONG TERM BOWEL

DYSFUNCTION AFTER ACUTE BRAIN INJURY

Introduction

There are scarce data on bowel dysfunction (BD) after brain injury (BI). Only the occurrence of fecal incontinence (FI) after the injury has received some attention. FI after BI has been associated mainly to the impact of brain damage on patient mobility and cognitive functions(5)(6)(7). However, data on this issue are scarce and other fecal incontinence precipitating factors such as the presence of diarrhea or liquid stools have not been taken into account before. Moreover, prevalence figures and, development of other types of bowel dysfunction different from FI after BI such as constipation, as well as its impact on QOL have not been previously evaluated.

Therefore, in this study we aimed to evaluate the prevalence, clinical characteristics, impact on QOL and risk factors of long-term clinically significant BD in patients that have experienced acute brain injury and are stabilized.

Materials and methods

Study Population

The study was approved by our IRB. Subjects with BI diagnosed ≥2 years prior to our evaluation who had finished their motor rehabilitation program, were not dependent on a ventilator and were capable of answering the interview by themselves were invited to participate. Patients with progressive or chronic neurological conditions were excluded.

Variables collected and Standardized Interview

Demographic information collected included date of birth and gender.

Clinical information collected included, artery/brain territory involved, date and etiology of injury.

At the time of the study all patients underwent a standardized interview that included the Barthel Index questionnaire (0-100)(27), questions on bowel function that included questions from validated questionnaires, such as the Bowel Disease Questionnaire(28), the Eating assessment tool (EAT-10) to screen for dysphagia (29) and the Bristol stool scale (30) and on perceived QOL (Which of the sequel you have experienced after your injury is affecting your QOL the most?. For each sequel, how has it impacted you QOL? on a scale of 0-3 (being 0=no impact, 1=some impact, 2= moderate impact and 3= high impact).

Diarrhea was defined as the presence of a Bristol scale score of 5-7. Syndromes such as constipation were defined based on validated Rome III criteria(31). Patients were considered having clinically significant Neurogenic Bowel Dysfunction (NBD) if they met Rome III criteria for constipation or referred weekly episodes of FI that appeared after their neural injury.

From responses to the questionnaire, we calculated the Neurogenic Bowel Disease Score(32) (<6 - NBDS very mild , $\leq$ 9 - NBDS minor and > 14 - NBDS severe). The FI Wexner score (0-20, 20 max. severity) and the constipation Wexner score (0-30, 30 max. severity) were used to assess the severity of incontinence and constipation, respectively(33)(34).

Data Analysis

Descriptive data are reported as percentages (%), for categorical variables, or means, for continuous variables (95% CIs).

To evaluate factors related to BI that might predict the presence of long term BD after the injury, we used logistic regression analyses. We explored if etiology, level of brain

territory affected (principal independent variables) predict the presence of NBD long-term after neural injury. Patients' sex, age and dependency (Barthel Index adapted score: excluding the two items on fecal and urinary incontinence) and presence of diarrhea were included as potential confounders since they are recognized risk factors for FI (35)(36)(37). Best-fitted regression models were selected on the basis of adjusted R^2 with the least number of independent variables. Odd ratios (OR) and their 95% CI from best-fitted models are reported.

Since most cases were of vascular origin in BI, the variable etiology was grouped in two categories, hemorrhagic and ischemic.

Results

Study population

During a period of 6 years, 381 patients with acute brain injury were admitted into the Rehabilitation Unit of Hospital del Mar and met the study inclusion criteria. We got response from 297 (78%). They were 58% males, with a mean age of 71 [69, 72] years old.

Etiology of Brain Injury and Barthel Index

Among the 297 cases, we could not elucidate the etiology in one patient, 288 cases (97% [95; 99]) were of vascular origin, 79% [75; 84] ischemic and 18% [14; 22] hemorrhagic. The cerebral arteries involved were the medial (MCA) in 179 (63% [57; 68]) cases, the vertebrobasilar in 39 (14% [10; 18]), the posterior (PCA) in 37 (13% [10; 17]), the anterior (ACA) in 10 (3.5% [1.9; 6.4]), the posterior-inferior (PICA) in 11 (3.9% [2.2; 6.8]), a miscellanea in 8 more cases (2.8% [1.4; 5.5]) and in 13 cases we could not elucidate the artery involved. The anterior-brain territory was affected in 189 (68% [63; 74] patients, the posterior in 87 (32% [26; 37]) and the basal ganglia (BG) were involved in 73 (28% [23; 34]) from which only 2 involved the thalamus.

On average, time passed since injury until our assessment was 4 years (3; 4) and the Barthel index was, 80 (77; 82).

Bowel Dysfunction

Table 1 shows the prevalence and clinical characteristics of the bowel dysfunction described by BI patients interviewed. Among the 297 patients a clinically significant proportion, 139 (47%) reported clinically significant bowel dysfunction. However, as assessed by the NBDS (2.3 [1.8; 2.9]) and the Barthel intestinal score (8.91 [8.6; 9.21]). the severity of their dysfunction was mild.

Constipation

Table 2 shows the specific clinical features of the constipation reported by the patients interviewed. For most BI constipated patients, it took between 10 to 20 minutes to clean the bowel. In 11 (10.5%) patients complete bowel evacuation was accomplished after 4 to 9 attempts to open their bowels. Overall, 55 (52%) patients needed some sort of help to move the bowels. To assist in bowel evacuation, laxatives were used in 45 (43%) of cases, rectal suppositories in 8 (7.6%) cases, digital stimulation in 9 (8.6%) and cleansing enemas in 3 (2.9%) cases. When rating the impact of constipation on QOL, 12 (11%) BI patients reported a "High impact", 41 (39%) a "moderate impact", 23 (22%) "some impact" and 29 (28%) patients reported that constipation had no impact on their QOL. Seven patients (7%) reported constipation being the worst sequel after their BI.

Fecal Incontinence

Among patients with FI, 24 (42%) reported to have incontinence episodes independently of their feces Bristol score. However, as observed in patients with FI in the community, the prevalence of FI was associated to higher Bristol scale stool scores (mushy or watery stool) (35) **(Figure 3)**. Thus, FI was more likely among patients who suffered diarrhea (36)(37). The median score on NBDS for FI, was 7 with a mean of 7.8 (6; 9), what translates into 1 to 6 incontinence episodes per week. Pads were used daily by 25 patients (53%) due to this problem and the average Cleveland Clinic FI-score (0-20) was 12,1 (11; 14). When rating the impact of FI on QOL, 15 (32%) BI patients reported a "High impact", 16 (34%) a "moderate impact", 10 (21%) "some impact" and 6 (13%) patients reported that FI had no impact on their QOL. One (2%) patient with BI, who was completely dependent for bath, and partially for transfers, stairs, toilet use, grooming and dressing and had also urinary incontinence, reported FI being the worst sequel of all.

Risk Factors for Long-Term Bowel Dysfunction after Neural Injury

The likelihood of reporting long-term FI after the BI was, in the univariate analyses, associated to age (p= 0.005), dependence score (p<0.0001), the presence of diarrhea (p<0.0001) and borderline associated to brain territory (p=0.07 and 0.14 for BG and posterior territory-excluding BG-affected) and to sex (p= 0.11). When adjusting for all these factors, the final model showed that the only factors that significantly influenced the likelihood of presenting FI independently of each other were patient's dependence score, the presence of diarrhea, involvement of BG or posterior brain territory. Thus, patients with greater dependence (OR per each unit decrement in the Barthel-adapted score: 36 [9.74; 142]; p<0.0001), with diarrhea (OR: 7.96 [2.80; 22.61]; p<0.0001) and those with BG (OR: 4.59 [1.90; 11.96]; p=0.001) or posterior territory – excluding BG-affected (OR: 3.00 [1.12; 8.34]; p=0.03) were more likely to report FI more than two years after injury.

The likelihood of reporting long-term constipation after BI was, in the univariate analyses, associated with patient's dependence scores (p= 0.002), anterior territory affected (p=0.02), and borderline associated with sex (p=0.08), but not with age (p= 0.45). When adjusting for all these factors, only dependence score (p=0.03) and anterior brain territory (p=0.02) remained in the model. Thus, patients with greater dependence (OR per each unit decrement in the Barthel-adapted score: 2.6 [1.1; 6.4]; p=0.03) and patients with anterior territory affected were more likely to report long-term constipation (OR: 1.9 [1.1; 3.3]; p=0.02).

Discussion

In this study we report on the prevalence, clinical features, impact on QOL and risk factors for developing bowel dysfunction in patients after acute brain injury. Our data show that around 50% of patients report some form of clinically significant BD more than two years after their acute neural injury.

The most frequent bowel complaints are those related to bowel emptying. Thus, significant constipation is reported by 35% BI patients. Abdominal pain and distention were also reported by a significant number of patients as well as FI. The latter was reported by 15% of patients with BI, similar that in patients with spinal cord injury.

Our estimation of long-term FI after BI is significantly greater than previously reported in these patients one year after injury (5)(6)(7). However, it is almost identical to the only study that has reported FI prevalence over a year after BI(7). Harari et al. reported 15% of FI in patients followed until 3 years after BI.

Relating to clinical traits of neurogenic bowel dysfunction, our data show that BI patients who develop constipation after injury mostly show clinical features of dissynergic defecation(38). Thus, overall, most patients report normal defecation frequency but need to strain excessively or fail to evacuate completely. Also, most of them report low volume and dry feces and abdominal distension. There are scarce data on pathophysiology mechanisms underlying neurogenic bowel after brain injury. Hence, we can mostly speculate regarding the potential differential mechanisms of constipation in this population. Injury of the upper motor neuron might conceivable cause impairment of colonic motor function which would facilitate abdominal distention through altered colonic compliance and lack of effective propulsive activity. Moreover, injury of upper motor neuron might also affect striated pelvic muscle (i.e. puborectalis muscle) control which would facilitate development of a defective defecation as observed in patients with altered pelvis muscle relaxation due to other causes(38).

Regarding FI development after the initial phase of injury, current data suggest that factors such as increased age, muscular weakness, impaired vision, sensation or cognition might explain the appearance of FI over time in patients after brain injury(6)(7). However, our prediction analyses suggest that beyond senescence factors suggested by Harari et al

(7) and even taking into account the presence of diarrhea(35)(36)(37), site of BI seem to have a significant influence on the likelihood of presenting FI on the long-term.

Interestingly, we observed patients with basal ganglia and posterior brain territory affected (vs. anterior territory affected) were more likely to report FI. There are two distinct pathways that process signals through the basal ganglia. These two pathways have opposite, excitatory and inhibitory, net effects onto cortical neurons (39)(40). Hence, a lesion at this level would alter the proper balance between these two pathways and may explain motor dysfunctions at the gastrointestinal level, causing altered colonic compliance, or anal sphincter tone, which may facilitate IF appearance when summed to other factors. In accordance with this hypothesis there are data that show decreased cortico-anal excitability (41). and increased activation of the caudate nucleus in patients that recover anorectal functions after sacral nerve stimulation (42).

We have also observed that patients with posterior brain areas affected, excluding basal ganglia are more likely to present FI compared to those with anterior circulation involved, who are more likely to report constipation. Most patients with anterior circulation involved had a stroke that affected the medial cerebral artery. Medial prefrontal area and the anterior cyngulate gyrus are involved in the voluntary control of defecation through spinal pathways(43). Thus, lesions in this area might explain difficulty opening the bowels or the voluntary control of anal sphincter. However, more in-depth studies on the different neurological and gastrointestinal mechanisms associated to bowel dysfunction will be needed to further clarify and confirm our findings.

Study Limitations

This study has some limitations; first it characterizes post- brain injury bowel dysfunction in patients from a referral hospital; thus, its conclusions might not apply in the general BI population. Also, this was a cross-sectional study; thus, the factors associated with the risk of presenting NBD, do not necessarily mean causation. Moreover, we cannot exclude other factors not controlled in this study might have confounded the observed associations.

STUDY 2 PHYSIOPATHOLOGY OF BOWEL DYSFUNCTION IN PATIENTS WITH BI COMPARED TO CONTROLS

Introduction

We have previously described that bowel dysfunction (BD) is highly prevalent and long-lasting after brain injury (BI) and is reportedly affecting patient's wellbeing. Most frequent bowel complaints in these patients are bowel emptying difficulty, abdominal pain and distention as well as fecal incontinence (FI). There are no data on the potential mechanisms underlying altered bowel functions in patients with BI. Data from our previous study show a relationship between brain area affected and the type of bowel dysfunction the patient may present. Therefore, suggesting a neurogenic cause of these gut dysfunctions. Thus, we planned the current study to compare the clinical characteristics of the gut dysfunctions presented by patients with BI and compare it to those presented by patients without BI. Also we aimed to evaluate motor and sensory functions in patients with post-BI BD compared to patients with similar clinical complaints but without BI.

Materials and methods

Study Population

The study was approved by our IRB. We invited to participate in this study subjects with BI diagnosed ≥2 years prior to our evaluation who had finished their motor rehabilitation program, were not dependent on a ventilator and who had participated in our previous study and were diagnosed of clinically significant BD (Post-BI BD). Patients with progressive or chronic neurological conditions were excluded.

Patients with severe dysphagia, as defined with a score > 3 in the Eating Assessment Tool (EAT-10), a validated tool to screen for dysphagia (29) were excluded since the study required swallowing of the WMC. All patients underwent the Barthel Index questionnaire (0-100) for assessment of their functional status at the moment of the study (27). Patients with severe cognitive or motion impairment were also excluded since the study required

informed consent, self-assessment of clinical variables, attendance to several clinical visits, and performing and consenting different study procedures.

As the control population, we invited to participate subjects (controls) without BI, SCI or any other neurological disorder, who presented similar clinical syndromes and who were sent by primary-care doctors to our GI Physiology and Motility lab for evaluation during the same time-period the patients with post-BI BD were recruited and studied.

Bowel Dysfunction

As in the first study of this thesis, diarrhea was defined as the presence of a Bristol scale score of 5-7(30). Syndromes such as constipation were defined based on validated Rome III criteria (31). Patients were considered having clinically significant BD if they met Rome III criteria for constipation(31), or referred weekly episodes of FI. In the case of BI patients, these symptoms appeared after their neural injury.

The severity of the BD was evaluated using the standardized and validated Wexner Scores for FI (0-20, 20 max. severity) and constipation (0-30, 30 max. severity)(33)(34).

Physiology Studies

Patients were invited to undergo a standardized physiological evaluation of their gastrointestinal motor functions at the GI Physiology and Motility Lab at Hospital del Mar. We evaluated gastro-intestinal and colonic motility and transit times with the Wireless Motility Capsule (WMC) and anorectal sensory and motor function using high-resolution anorectal manometry. Patients also underwent a complete study at the Neurophysiology Unit of the Hospital, which included electromyography of pelvic muscles, study of sacral reflexes and the perineal cutaneous-sympathetic responses and study of long cortico-spinal tract function to exclude peripheral and central neuropathies.

Wireless motility capsule (WMC) test procedure

Patients were told to attend the GI Physiology and Motility lab in the morning after an overnight fast. Patients were advised to discontinue all drugs that might influence GI motility such as prokinetics, antidiarrheals, and laxatives as well as histamine receptor

antagonists, and antacids for 72h prior to the test. Proton pump inhibitors were discontinued 7 prior to the test.

After obtaining written informed consent participants were asked to consume a standardized SmartBar (260 kcal, 2% fat, 1 g fiber) (Given Imaging, Israel) with 120 ml of water. The patient was then instructed to swallow the WMC with the aid of 50 ml of water. Successful swallowing of the WMC was confirmed by checking the pH on the small lightweight portable external recorder. This recorder was given to the patients who were reminded it would need to be kept no more than 30cm apart from the patient's body throughout the study period to ensure appropriate data recording. Patients were also explained they should avoid eating for another 6 h and afterwards they could resume their normal daily activities. After this patients were discharged and told to come back when the expulsed the capsule or 7 days after discharge.

With WMC we evaluated: the gastric emptying time (GET), the small bowel transit time (SBTT), the colonic transit time CTT) as well as the motility index (MI, the frequency and amplitude of the contractions as well as the area under the curve (AUC) of the stomach and small bowel as previously estandardized and reported in the literature (17)(18)(19)(20)(21)(22)(23).

High Resolution Ano-rectal Manometry

As explained before we evaluated anorectal function using ano-rectal manometry. Prior to the test (2 hours before) the patient had evacuated the rectum with the use of an intrarectal stimulant. The patient did not need to be fasting before the test. Before carrying out the study and to encourage collaboration, the patient was explained the maneuvers that he or she would be asked to do during the test .

Before starting the study, the equipment was calibrated. Then, with the patient placed in left lateral decubitus position, the catheter was inserted through the anal canal . After a period of adaptation of about 3-5 min, the test was started.

We evaluated the anal canal resting pressure (RP) during two periods of 30 seconds, the pressure of maximum voluntary contraction (VCP), from two manoeuvres, duration of voluntary contractions and the rectoanal inhibitory reflex (RAIR).

To evaluate rectal sensitivity we programmed a continuous inflation of the intrarectal balloon and asked the patient to report when he or she felt 1st sensation (S1), the desire to defecate (S2) the urge to defecate (S3) and the imperative need to defecate (S4). We evaluated adequate reflex contraction of the external anal sphincter requesting the patient to cough 3 times.

Data Analysis

Data from WMC studies

Gastric emptying time (GET) was defined as the time from ingestion of the WMC to an abrupt and sustained rise in pH by 2.0 units from the gastric baseline to pH

Delayed GET was defined as > 4h, as previously reported. (17).

Small bowel transit time (SBTT) was defined as the time from exit from the stomach, as detailed above, to a sharp drop in pH of 1.5 units as the WMC passes the ileo-caecal valve into the colon.

Delayed SBTT was defined as > 6h, as previously reported. (17).

Colonic transit time (CTT) was defined based on entry of the WMC into the colon until expulsion of the capsule from the body as denoted by a drop in the temperature as it enters the external environment.

Delayed CTT was defined as > 59h, as previously reported. (17).

We calculated, for the stomach and the small bowel the motility index (MI) in units of mmHg as the summation of areas under the curve (computed as the amplitude of the reading multiplied by the duration of that reading) divided by the time of the entire window, according to the formula used by Ouyang, et al. (44). Area under the curve was computed only for those contractions 10 mmHg above baseline. We report as well the frequency and amplitude of contractions in each segment.

Data from Ano-Rectal HRM studies

The variables recorded for anorectal function were length of the anal canal (mm), maximun anal basal pressure (mmHg), maximum mean anal basal pressure (mmHg), maximum anal contraction pressure (mmHg), maximum mean anal contraction pressure (mmHg), duration of maintained contraction (seconds), rectoanal inhibitory reflex (RAIR) (yes/no), RAIR (cc), reflex anal contraction with Valsalva manoeuvre (yes/no), abdominal contraction during defecation (yes/no), anal relaxation during defecation (yes/no), S1-S3 (cc).

Statistical Analysis

We have reported descriptive data as percentages (%), for categorical variables, and means, for continuous variables (95% CIs).

Comparisons between the two groups, post-BI BD and controls were performed using ANOVA adjusted by sex for continuous variables and logistic regression for binarial variables. We report Least Square Means (Standard Error of the Mean) and adjusted Odd ratios (OR) and their 95% CI for continuous and binarial variables, respectively.

Results

Study Population

We evaluated eighty-nine patients that met the study criteria. From these, 42 had post-BI bowel dysfunction, and 47 were controls with BD without brain or any other neurology impairment. All of them agreed to undergo a standardized clinical workup as detailed above.

Brain Injury Patients

There were 21 females and 21 males, with a mean age of 69 [66; 72] years old. The 42 patients had experienced an acute brain event. 32 (76%) ischemic stroke, 9 (22%) hemorrhagic stroke and 1 (2%) post-surgery. On average, time from the acute brain event

until the study was 3 [3; 4] years and the Barthel index was 80 (75; 85). Their Neurogenic bowel disease score was 6 [4; 8].

Table 3 shows epidemiological data as well as BI characteristics separated by type of BD syndrome.

Control Patients

There were 41 (87%) females and 6 (13%) males, with a mean age of 64 [60; 67] years old. All of them were excluded to have BI or SCI based on clinical history.

Table 3 shows epidemiological data as well as BI characteristics separated by type of BD syndrome.

Medication

Medications taken by the BI patients and controls were collected.

The medications that patients were using at the time of the study were grouped as antidepressants, benzodiazepines, anticonvulsants, laxatives, prokinetics, thyroid hormones, proton pump inhibitors (PPI), opioids, anticholinergics, antispasmodics, oral iron, NSAIDs, calcium, beta blockers (BB) and other.

Table 4 shows the proportion of patie nts reporting use of each medication type by patient group. There were no differences on drug use between groups under comparison.

Bowel Dysfunction

Among the 89 patients evaluated, 46 met the study criteria for clinically significant constipation and 43 of fecal incontinence (FI). **Tables 5** and **6** shows the clinical details of these two major syndromes in both post-BI BD and controls.

Constipation

Table 5 shows the comparison of the clinical features of the constipation reported by BI patients and controls. As expected, BI patients reported a shorter period of time with constipation compared to controls (p=0,002) since constipation appeared after their BI. Thus, in BI patients the length of time with constipation was 1yo [1; 2] and in controls patients was 2yo [2; 3]. For a BI constipated patients, features of obstructed defecation

(straining > 25% of time, > 30 minutes to evacuate, failed evacuation or need of evacuation maneuvers) were as frequent as in the control population. However, among constipated BI patients it was more frequent to report a decreased number of bowel movements, as defined by ≤ 1 bowel movement a week, compared to controls (p=0,0002). Moreover, BI patients presented less frequently than controls the feeling of complete evacuation (p=0,0002) and abdominal pain (p=0,0008) as well as lower Wexner scores. Thus, the mean of Wexner score constipation was 10 [8; 11] in BI patients and 13 [12; 15] in controls (p=0,003).

Fecal Incontinence

Table 6 shows the comparison of the clinical features of the fecal incontinence (FI) reported by BI patients and controls. The clinical distinctive features between BI patients and controls were the higher prevalence of liquid feces in BI patients (p=0,03) as well as the presence of FI associated to solid feces also more frequently (p=0,03), what might suggest a more severe FI. However, we found no differences in Wexner scores reported by both groups (p=0,08). the mean of Wexner score FI was 10 [8; 12] in BI patients and 8 [6; 10] in controls (p=0,003). Tehre were 2 patients with BI who reported FI with solid stools and the two of them were partly dependent for toilet use and trasnfers, which may explain this difference.

The impact on QOL was similar in both groups (p=0,6). When rating the impact of FI on QOL, 4 (9%) BI patients reported a “High impact”, 7 (17%) a “moderate impact”, 5(12%) “some impact” and 26 (62%) patients reported that FI had no impact on their QOL.

Bowel physiology studies: comparison between BI and controls.

Stomach and Small Bowel Function

There were 2 patients in the control group and 6 in the BI groups that did not undergo the WMC studies. In the group of patients with BI this was due to the presence of dysphagia with EAT >3; in the case of the control group 2 subjects did not show to the WMC appointments.

Gastric transit time was increased in 38% of BI patients with constipation compared to 16% of constipated controls (p=0.096). The OR $_{\text{adjusted by sex}}$ of having prolonged GET in controls vs BI patients was 0,23 [0,04; 1,26], p=0.096. Motor phasic activity, as measured by frequency and amplitude of contractions was reduced in constipated BI patients compared to constipated controls, although these differences did not reach statistical significance. **(Table 7)**

No differences were observed in small bowell transit times between both groups. Prolonged SBTT was detected in 36 and 38 (p>0.05) of BI and control groups, respectively. On average, amplitude of contractions were reduces in the small bowell of BI constipated patients compared to constipated controls (p=0.018). **(Table 7)**

Table 7 shows the stomach and small intestine motor parameters as measured with de WMC in constipated patients and **Figure 4** pictures an example of stomach and small bowel WMC tracings in BI an control patients.

Colonic Function

Colonic transit was delayed in 50% of BI patients with constipation compared to 44% of constipated controls (p>0.05).

Ano-Rectal Function

Table 8 and **9** shows high resolution anorectal manometry parameters in both study groups.

In constipated patients HRM showed increased rectal volumes needed to trigger the RAIR. RAIR in patients with BI (18cc [13; 24]) vs. Controls (11cc [10;12]); p = 0.002. (Figure 6). The rectal volumes need for first perception, defecation perception and urgency were higher than the control group but differences did no reach statistical significance **(Table 8)**

Compared with controls with FI, patients with BI and FI presented shorter anal 3,2 cm [2,8;3,5] vs 3,6 cm [3,2;3,9]; p = 0.01 and lower pressure contraction 132[107;156] vs 145 mmHg [114,176]; p = 0.06. (Figure 7 and 8). The rectal volumes need for first perception, defecation perception and urgency were also higher in BI partients with FI

compared to the controls with FI; however, differences did no reach statistical significance **(Table 9)**

The other anorectal parameters measured were similar in both groups.

Discussion

In this study we report on clinical manifestations and GI motor physiology parameters of patients that developed bowel dysfunction after BI and maintained it at the moment of the study, after at least 2 years from the brain event. We compared them to a sample of patients, who had not suffered any brain injury and were free of any other relevant neurological disease or impairment. Our hypotheses were that patients that develop BD after BI have underlying neurogenic mechanisms that are not present in the general population presenting with BD. Thus, we aimed to compare clinical features and physiological measurements of BD in BI and control patients.

One of the main study findings is that patients who develop constipation after BI have few differentiated clinical characteristics compared to constipated controls. As our data suggest, BI patients show increased odds for presenting fewer bowel movements per week, and decreased odds for reporting abdominal pain associated to their constipation and feeling of incomplete evacuation. On the other hand, other clinical features of obstructed defecation such as straining, > 30 minutes per evacuation, number of failed intents or need of digitation maneuvers were not different between BI patients and controls.

In this regard the HR anorectal manometry performed in these patients showed that BI patients with constipation needed higher rectal volumes to trigger the RAI reflex compared to constipated controls. This might be related to decreased rectal wall tone or increased rectal volumes, as is observed in chronic constipation patients(45)(46)(47). It might also be related to decreased rectal visceral sensation. There it seems plausible that patients with BI may present, due to the brain damage, suboptimal central integration of visceral sensory signals (48)(9). This would conceivably decrease their perception of visceral events such as rectal filling or the presence of abdominal pain as was observed in this study.

As we have explained above, BI patients with constipation had increased odds for presenting fewer bowel movements as compared to constipated controls. One can speculate that this might be related to decreased mobility or even differences in water or fiber intake. We did not control for these variables; hence, we cannot exclude these potential confounders. However, we were very careful to include patients with BI with a good performance status and with good mobility. Therefore, we do not expect that mobility and water or fiber intake would be significantly different between the two study groups. Also, we reviewed the medications of the two populations and did not find differences between BI and controls patients. On the other hand, the WMC studies revealed that BI patients with constipation had higher odds of presenting delayed transit and or motor activity affecting the stomach, the small bowel compared to constipated controls. Although the patients evaluated in this study represent a small sample we hypothesize that BI patients that develop clinically significant constipation might actually have a different underlying mechanism as the one present in constipated controls from the general population. Thus, as observed in the first study of this thesis, patients who present injury in the anterior brain territory has more odds of developing long-term clinically significant constipation. Hence, it would not be unconceivable that lesion of the upper motor neuron in these patients may partly explain the decrease in bowel motility indexes explored in this study. Further studies will be needed to confirm this hypothesis.

Regarding fecal incontinence, our data shows that compared to control patients with FI, BI patients who develop and maintain FI years after the brain event, present higher odds for reporting incontinence to gas, liquid and solid feces. Our data also show that BI patients with FI present as well higher odd for diaper use. These comparisons were adjusted by differences in sex, since the latter is known to influence FI severity (49)(50). Moreover, BI patients with FI that participated in this study had a very good performance status with good mobility and high Barthel scores and a similar age compared to FI control patients. Thus, these differences cannot be explained by global impairments associated with injury severity as is currently stated (6).

An alternative hypothesis might be that, as we stated at the beginning of this study, differences on clinical traits would be related to differences in the underlying mechanisms of FI between the two groups. The results of the anorectal manometry would actually

support this hypothesis since the length and the pressure during voluntary contraction of the anal canal were lower in BI patients as compared to controls.
How could we explain this decreased anal canal functional length as well as the decreased pressure in the anal canal during voluntary contraction in BI patients compared to controls? In the first study presented in this thesis we described that patients with injury in the posterior brain territory and basal ganglia had more odds of developing FI. One putative hypothesis might be that injury of the upper motor neuron or altered activation of caudate nucleus might partly explain FI in these patients (39)(40)(41)(42).

In conclusion,

In this study we studied cpmpared clinical features of bowel dysfunction presented by patients who had suffered from Bi and a group of controls with similar clinical complaints and age. The results will need to be replicated in future and bigger studies. However, they would support for the first time the hypothesis that constipation and fecal incontinence developed after BI might actually be pathophysiologically explained by the brain area injured, which seem to alter gastro-intestinal and colonic function in these patients.

CONCLUSIONS

We analyzed on the prevalence, clinical features, impact on QOL and risk factors for developing bowel dysfunction in patients after acute brain injury and clinical manifestations and GI motor physiology parameters of patients that developed bowel dysfunction after BI and maintained it at the moment of the study, after at least 2 years from the brain event.

Our conclusions are:

1. Our data show that around 50% of patients report some form of clinically significant BD more than two years after their acute neural injury mostly show clinical features of dissynergic defecation and the most frequent bowel complaints are those related to bowel emptying.

2. Our data show that BI patients who develop constipation after injury mostly show clinical features of dissynergic defecation.

3. Our prediction analyses suggest that site of BI seem to have a significant influence on the likelihood of presenting FI on the long-term. We observed patients with and excluding basal ganglia and posterior brain territory affected were more likely to report FI and patients with anterior circulation involved, were more likely to report constipation.
4. Our data suggest, BI patients show increased odds for presenting fewer bowel movements per week, and decreased odds for reporting abdominal pain associated to their constipation and feeling of incomplete evacuation.
5. Obstructed defecation such as straining, > 30 minutes per evacuation, number of failed intents or need of digitation maneuvers were not different between BI patients and controls.
6. HR anorectal manometry performed in these patients showed that BI patients with constipation needed higher rectal volumes to trigger the RAI reflex compared to constipated controls.

7. WMC studies revealed that BI patients with constipation had higher odds of presenting delayed transit and or motor activity affecting the stomach, the small bowel compared to constipated controls.
8. Our data shows that compared to control patients with FI, BI patients who develop and maintain FI years after the brain event, present higher odds for reporting incontinence to gas, liquid and solid feces present as well higher odd for diaper use.
9. HR anorectal manometry performed in these patients showed that the length and the pressure during voluntary contraction of the anal canal were lower in BI patients with FI as compared to controls.

TABLES

Table 1. Study 1. Prevalence and clinical presentation of BD after BI

Brain injury	N=297 % [95% CI]
Bowel Dysfunction	47 [41; 52]
Rome-III Constipation	35 [30; 41]
Abd. Distention	27 [23; 33]
Abd. Pain	16 [12; 20]
Fecal Incontinence	16 [12; 20]
Dysphagia	24 [19; 29]

Table 2. Study 1. Clinical features of constipation in BI patients

Brain injury	**N=105** **% [95% CI]**
Difficult evacuation/Straining	97 [92; 99]
Incomplete evacuation	79 [70; 86]
Bristol 1-2	66 [55; 80]
Abdominal Pain	21 [14; 30]
Absence Defecation Sensation	0.95 [0.17; 1.0]
Abdominal Distention	44 [35; 53]
<3BM/ week	18 [12; 27]
<10 min evacuation	9.5 [5.3; 17]
10-20	84 [67; 100]
>20 minutes evacuation	6.5 [2.5; 17]
Wexner Score	8.3 [7.5; 9.1]

Table 3: Study 2. Study population: Epidemiological and BI data

Constipation	BI (N=20)	Controls (N=26)	FI	BI (N=22)	Controls (N=21)
Gender	60% M	88% F	**Gender**	59% F	86% F
Age (yo)	67 (62; 72)	62(58; 67)	**Age (yo)**	71 (67; 75)	65 (60; 71)
Ictus	95%	--	**Ictus**	100%	--
Years since BI	3,2 (2,4; 4,0)	--	**Years since BI**	2,6 (2,1; 3,2)	--
Barthel	81.5 (73; 90)	95(83; 100)	**Barthel**	78 (71; 85)	90 (85; 100)
NBDS	3 (2; 4)	--		8,5 (6; 11)	--

Table 4: Study 2. Use of medications in BI patients and controls

MEDICATION	BI (N=20)	Controls (N=26)	p
Antidepressants	41%	34%	0.36
Benzodiazepines	34%	28%	0.32
Anticonvulsants	15%	13%	0.54
Laxatives	10%	15%	0.96
Prokinetics	2%	2%	0.94
Thyroid hormones	5%	9%	0.93
PPI	71%	43%	0.82
Opioids	10%	10%	0.18
Anticholinergics	0%	2%	0.97
Antispasmodics	0%	2%	0.97
Oral iron	12%	2%	0.24
NSAIDS	5%	13%	0.83
Calcium	10%	11%	0.18
Betablockers	20%	11%	0.85
Other drugs of action in the CNS	22%	15%	0.33

Table 5: Study 2. Constipation clinical traits in BI and controls

Constipation	BI (N=20)	Controls (N=26)	p (sex adj)
Years with constipation <5	80%	39%	0,002
≤ 1 bowel movement/week	35%	11.5%	0.0002
Straining > 25% of time	60%	73%	0.76
> 30 mins /evacuation	0%	8%	0.8
Failed evacuations (never/ > 4 times x day)	50% / 15%	58%/ 0%	0.8
Need digitation / enema	80%	65%	0.2
Feeling of incomplete evacuation	20%	81%	0.0002
Abdominal Pain	15%	83%	0.0008
Wexner score(0-30)	9(1)	14 (1)	0.003

Table 6: Study 2. Fecal Incontinence clinical traits in BI and controls

Every day or every week Fecal incontinence	BI (N=22)	Controls (N=21)	p (sex adj)
Gas	36.4%	9.5%	0,14
Liquid faeces	22.7%	9,5%	0.03
Solid feces	18,2%	4.7%	0,03
Diaper use	36.4%	14,3%	0.05
Quality of life affected	36.4%	28,6%	0.6
Urgency	86%	95%	0.99
Anti-diarrheal drug use	4,5%	4.8%	0.98
Wexner Score (0-20)	9,78 (1)	7,39 (1)	0.08

Table 7: Study 2. Stomach and Small Intestine motor parameters measured with de WMC in constipated BI patients and constipated controls

	BI (N=20)	**Controls (N=26)**	**p (sex adj)**
STOMACH (GW)			
Contractions / h	84 (42)	160 (36)	0.18
Amplitude	14	22	0.11
AUC	3780 (1937)	7146 (1649)	0.20
MI	63 (12)	119 (27)	0.09
SMALL BOWEL (SW)			
Contractions / h	255 (51)	200 (46)	0.44
Amplitude	11(2,2)	19 (2)	0.018
AUC	9216 (2286)	8132 (2030)	0.73
MI	135 (34)	154 (38)	0.73

GW: Gastric Window. SW: Small bowel Window. AUC: sum of the amplitude of the contractions during the reading multiplied by the duration of that reading. MI: the summation of areas under the curve divided by the time of the entire window

Table 8: Study 2. High resolution anorectal manometry parameters in constipated BI patients and constipated controls

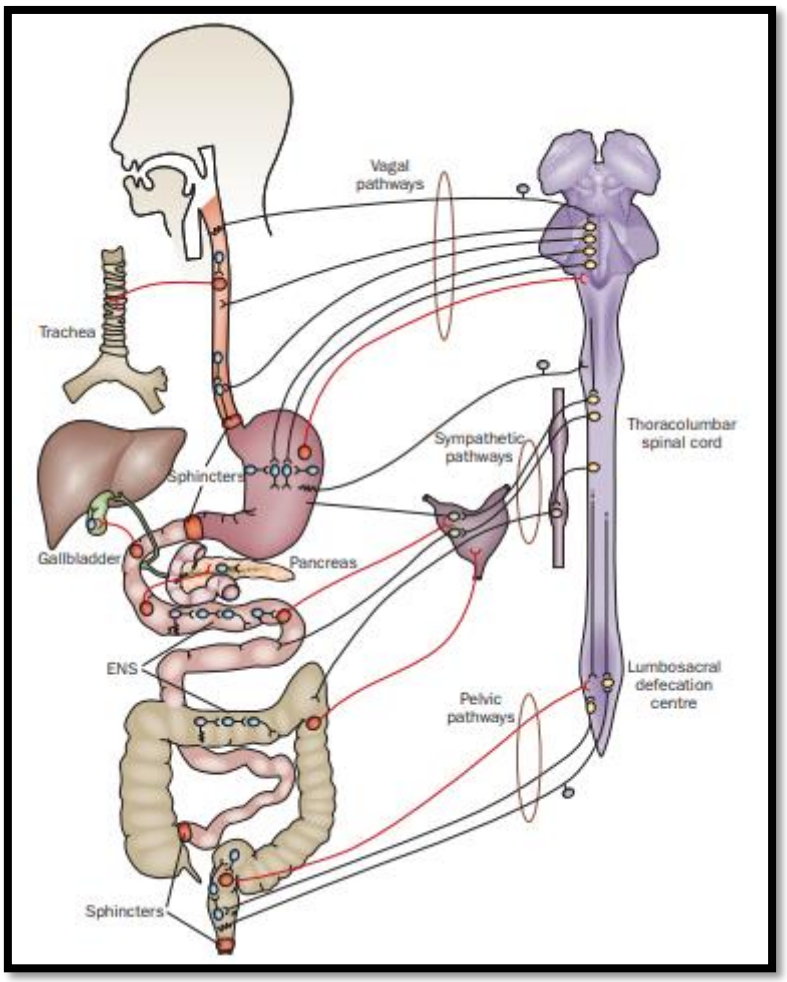
Constipation	**BI (N=20)**	**Controls (N=26)**	**p (sex adj)**
Anal canal Length (cm)	3 [3; 4]	5 [2; 8]	NS
Max anal basal pressure (mmHg)	60 [54; 67]	65 [57; 74]	NS
Max mean contraction pressure (mmHg)	177 [141; 212]	157 [133; 182]	NS
Duration of maintained contraction (seconds)	23 [19; 27]	25 [21; 29]	NS
RAIR (cc)	18 [13; 24]	11cc [10;12]	**0.002**
Reflex anal contraction with Valsalva manoeuvre (%YES)	100%	96%	NS
Anal relaxation during defecation	36%	40%	NS
First Sensation (cc)	93 [64; 122]	72 [56; 89]	NS
Desire to defecate (cc)	181 [147; 214]	167 [129; 205]	NS
Urgency (cc)	236 [187; 284]	212 [165; 260]	NS

Table 9: Study 2. High resolution anorectal manometry parameters in BI patients and controls with FI

Every day or every week Fecal Incontinence	**BI (N=22)**	**Controls (N=21)**	**p (sex adj)**
Length anal canal (cm)	3.2 [2,8;3,5]	3.6 [3,2;3,9]	**0.01**
Max anal basal pressure (mmhg)	60 [52; 69]	57 [50; 64]	NS
Max anal contraction pressure (mmhg)	132[107;156]	145 [114;176]	**0.06**
Duration of contraction maintained (seconds)	26 [19; 34]	21 [17; 25]	NS
RAIR (cc)	16 [13; 19]	12 [10; 14]	NS
Reflex anal contraction with Valsalva manouver (% yes)	100%	100%	NS
Anal relaxation during defecation (%YES)	40%	90%	NS
First Sensation (cc)	83 [58; 109]	74 [53; 96]	NS
Desire to defecate (cc)	143 [106; 180]	114 [89;139]	NS
Urgency (cc)	235 [179; 291]	204 [171;236]	NS

FIGURES

Figura 1: Gut-Brain Axis



Obtained from Furness JB. The enteric nervous system and neurogastroenterology. Nature Reviews Gastroenterology and Hepatology. 2012.

Figura 2: Wireless motility capsule (WMC)

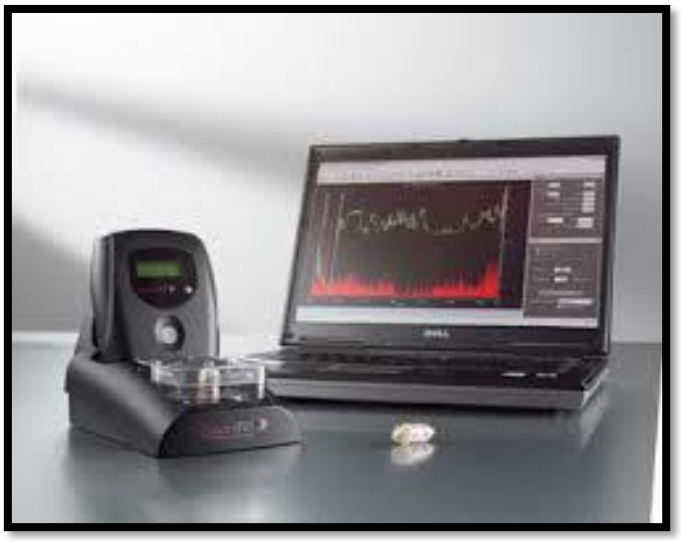


Figure 3: Percentage of BI patients reporting FI by feces Bristol scale categories.

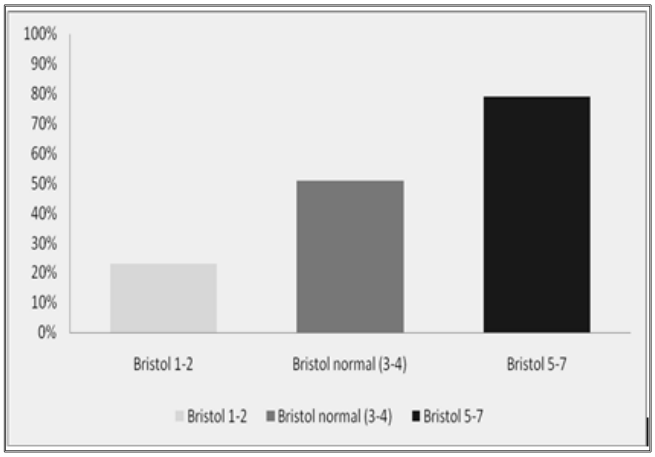


Figure 4: Examples of transit times and MI in the Stomach & Small Bowel in controls and BI patients

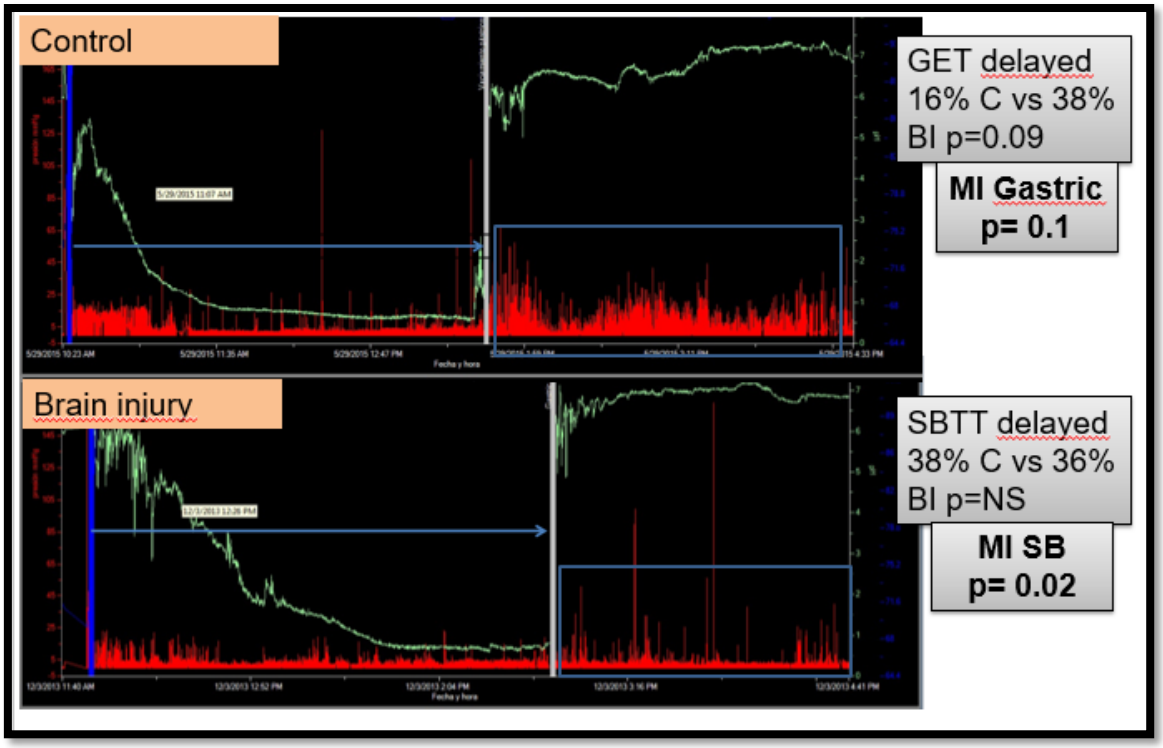


Figure 5: Examples of Transit times in controls and BI patients

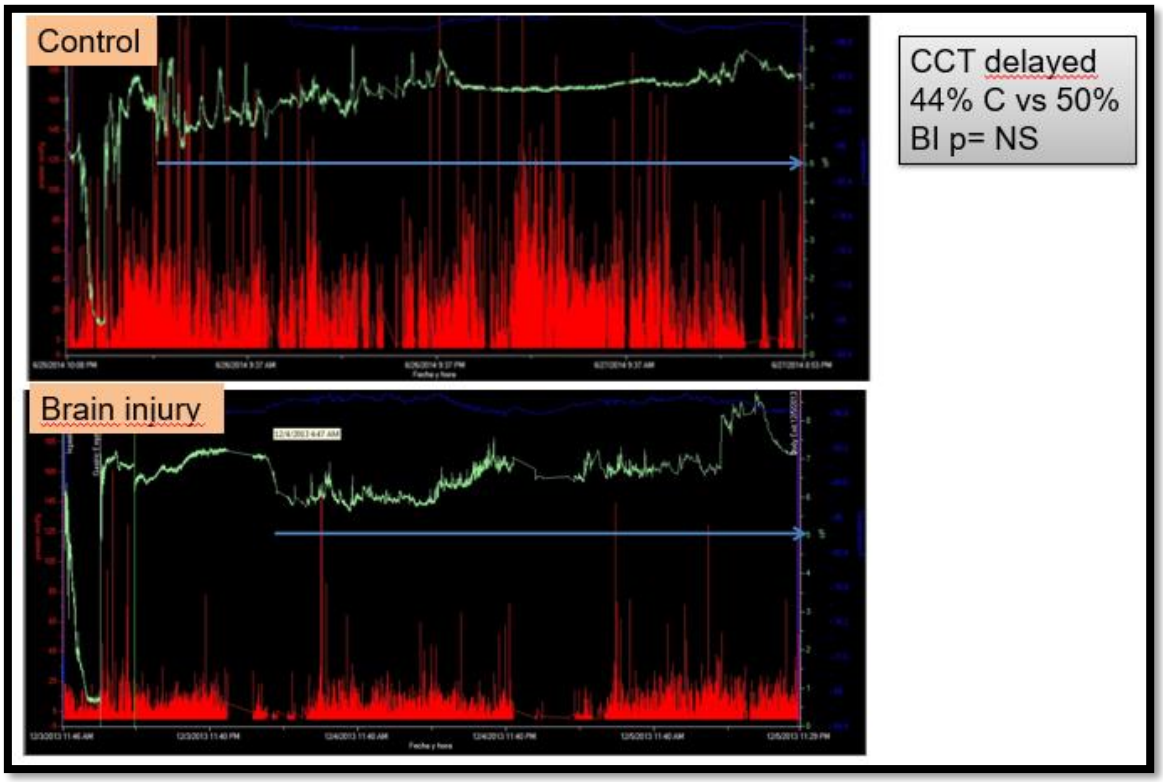


Figure 6: RAIR in BI constipated patients and constipated controls

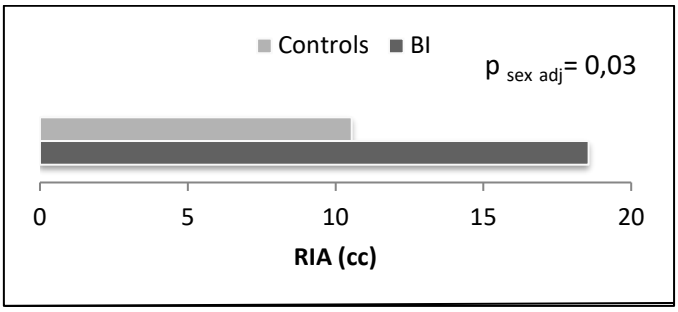


Figure 7: Anal canal length in BI patients and controls with FI

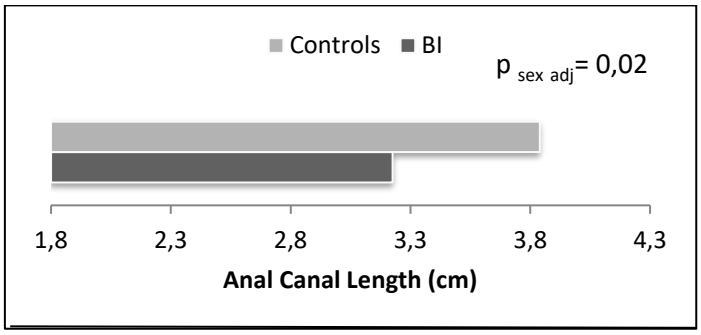
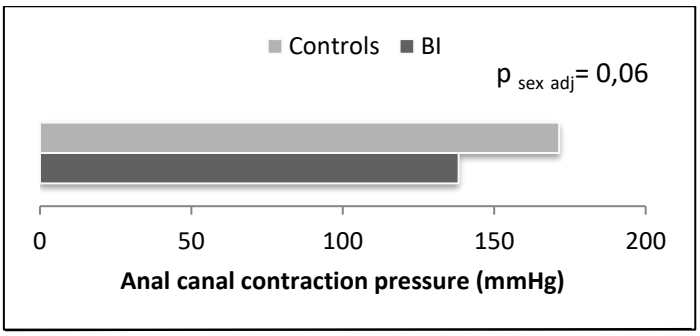


Figure 8: Anal canal contraction pressure in BI patients and controls with FI



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