Constipation in Multiple Sclerosis

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ABSTRACT

Constipation and faecal incontinence are a relatively common problem in people with Multiple Sclerosis (pwMS) significantly affecting patients' quality of life.

Constipation involves several symptoms and factors over and above the infrequency of bowel movements. Therefore an individualized approach to constipation would be always recommended since a combination of factors such as poor diet, reduced or lack of physical activity and depression may affect the digestive system of pwMS. Medications and supplements may also contribute to constipation, considerably affecting patients' quality of life. The topic for this clinical audit will be to establish the frequency and significance of faecal incontinence and constipation, including associated risks factors among pwMS at Barts Health.

Participants were requested to complete a series of questionnaires addressing demographic and clinical data, including the Constipation Score for evaluation of constipated patients; the symptoms and Quality of Life questionnaires for assessing and evaluating patient-reported constipation over a period of time; the Physical Activity questionnaire to find out about patients fitness status; the Incontinence score designed to measure patients' perception on bowel control; the Hospital Anxiety and Depression Scale designed to help doctors to understand how patients felt regarding their condition; the Food and Drink diary to assess whether they were meeting the recommended servings and nutritional intake; and the Bowel diary incorporating Bristol Stool Scale to examine their bowel movement habits.

It is hoped that this preliminary data will stimulate new avenues for investigation as the effects of nutrients on constipation and well being of patients with MS continue to be revealed.

As a result of this audit, a service specifically focussing on bowel function in pwMS could be developed to educate and empower patients to self-manage, improve their nutrition and quality of life and avoid acute hospital admissions (due to constipation) leading to saving for the UK National Health Service.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory and degenerative disease of the central nervous system (CNS) affecting over 120,000 people in the UK ⁽¹⁾ and 2,500,000 people worldwide ⁽²⁾. The aetiology of MS is not well understood but it is likely to be a combination of both genetic and environmental factors ⁽³⁾. Pathologically, MS is characterized by focal de- and remyelination, neuro-axonal loss, and gliosis. The course of MS is variable, depending on the individual's pattern of demyelination. Symptoms range from numbness and tingling to blindness and paralysis, including balance and mobility impairments, weakness, reduced cardiovascular fitness, ataxia, fatigue, bladder dysfunction, spasticity, pain, cognitive deficits and depression ⁽⁴⁾. Onset is most usually in the third or fourth decade of life, but first symptoms can occur at any age in adulthood. Early symptoms can be mild, intermittent and ambiguous, and there may be considerable delay between the onset of symptoms and a definitive diagnosis. Several patterns may be distinguished, the three main types being: Relapsing-remitting, Primary-progressive and Secondary-progressive ⁽³⁾.

Constipation and faecal incontinence are considered a common problem in patients with Multiple Sclerosis (pwMS) with a significant impact on their quality of life ⁽⁵⁾. According to the Hospital Episode Statistics data (HES), constipation is also the fourth most common cause of hospitalization in pwMS. Constipation occurs when

bowel movements become difficult or less frequent than usual. The frequency or time between bowel movements ranges widely from person to person. Some people have bowel movements several times a day while others only one to two times a week. Having an infrequent bowel movement (i.e. more than three days) is considered too long ⁽⁶⁾. However, currently we have no detailed data on the management of this problem, and thus no way to establish the frequency and complexity of constipation and faecal incontinence in pwMS. There is insufficient information on the factors contributing to or modulating this problem.

Constipation is a common condition among people with MS. A combination of factors such as poor diet, reduced or lack of physical activity and depression may affect the digestive system of pwMS. Medications and supplements may also contribute to constipation, considerably affecting patients' quality of life.

OBJECTIVES

In order to explore the significance of constipation in pwMS and the impact of bowel symptoms 100 MS outpatients from the patient infusion unit (PIU) Neurology Ward at The Royal London Hospital (RLH) were recruited. Participants were asked to complete a series of questionnaires¹ as means to elucidate constipation prevalence, describing its symptoms, giving detailed account on their quality of life, including questions on their physical activity. Patients' perception on bowel control was also noted. Patients were also screened using questionnaires to described how they perceived anxiety and depression. The Audit also analysed the food and drink habits of patients enrolled, in order to track whether they were meeting recommended servings and nutritional intake. To examine the bowel movements habits of patients enrolled in the study, data collected with the Bowel Diary (incorporating the Bristol stool scale) was analysed.

METHODS

We recruited 100 outpatients from the PIU Neurology ward and MS clinic, at the RLH, between March and May 2015. A total of 85 Patients participating in the audit were interviewed during their scheduled monthly infusions of Natalizumab² or Fingolimod³. Further 15 patients were recruited during routine follow-up visits to their MS clinic.

The inclusion criteria to be eligible for the study was to be age 18 or above, female or male, and have been clinically diagnosed with Multiple Sclerosis by a RLH MS consultant. Exclusion criteria applied to patients identified by nurses as having cognitive impairments (as a result of MS).

¹ Appendix-1: Questionnaires (available on request).

² Natalizumab, an a₄-integrin antibody used for the treatment of MS. It is given as a 300 mg dose administered over 1 hour every 28 days [Internet]. Further information available at: http://www.tysabrihcp.com/pdfs/IV_Infusion_Guidelines.pdf

³ **Fingolimod**, a 1-phosphate receptor modulator indicated for the treatment of patients with RRMS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability [Internet]. Further information available at:

https://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf.

Participants were requested to complete a series of questionnaires addressing demographic and clinical data, including the Cleveland Clinic Constipation Score (CCCS) ⁽⁷⁾, Patient Assessment of Constipation Symptoms (PAC-SYM) ⁽⁸⁾, Patient Assessment of Constipation Quality of Life (PAC-QoL) ⁽⁹⁾, International Physical Activity Questionnaire Short Form (IPAQ-SF) ⁽¹⁰⁾, St Marks Incontinence score ⁽¹¹⁾, Hospital Anxiety and Depression Scale (HADS) ⁽¹²⁾, Food and Drink diary, and Bowel diary incorporating Bristol Stool Scale ⁽¹³⁾.

Data collected from questionnaires and Bowel diary was compiled in Excel and spreadsheets were populated accordingly. Data collected from the Food & Drink diary was analyzed using Dietplan6 (nutrition analysis software)⁽¹⁴⁾. The data analysis has been presented as frequencies, means, medians and ranges.

RESULTS

Patients characteristics

A total of hundred outpatients with Multiple Sclerosis (37 male and 63 female), with a median age of 39 (range 22-63 years), were interviewed at the PIU Neurology ward, RLH (Table-1).

Interviews took place over a period of 20 working days (from 30th March to 19th May 2015). Patients were given a series of standard questionnaires (Table-3) designed to gather information to define symptoms of constipation; the impact of constipation in their quality of life; the intensity of physical activity patients carried out in a given week; their perception on bowel control; and their perceived anxiety and depression as a result of MS. Patients also completed a weekly Food and Drink diary to evaluate whether they were meeting the recommended servings and nutritional intake, and a weekly Bowel diary to examine their bowel movement habits.

The study group comprised 84 patients with relapsing-remitting Multiple Sclerosis (RRMS) receiving their monthly intravenous infusions of Natalizumab; 1 patient with highly active RRMS was receiving her first treatment with Fingolimod; and a group of 15 patients were attending a routine outpatient appointment at the MS clinic, RLH.

Patients experiencing difficulties holding a pen and writing due to MS (n=12) were offered to complete an electronic version of all questionnaires, however only 3 patients returned the completed forms.

The overall response rate of completed questionnaires was 82.75%. In addition, 18,5% of respondents completed the Food & Drink and Bowel diaries (Table-2).

Data analysis

Questionnaires and Bowel diary data have been presented as frequencies, means, medians and ranges. Data collected from the Food & Drink diary was analyzed using Dietplan6 nutrition analysis software⁴.

⁴ Appendix-2, Dietplan6 output (available on request).

Gender	(n=100)				
Female	63				
Male	37				
Age dist	tribution	Number of			
(Ye	ars)	patients			
20	-29	25			
30	-39	31			
40	-49	25			
50	-59	16			
60	-63	3			
Treat	ment	Number of patients			
Natali	zumab	84			
Fingo	limod	1			

Questionnaires	Returned
CCCS	(n=79)
PAC-SYM	(n=83)
PAC-QoL	(n=82)
St Marks	(n=75)
IPAQ-SF	(n=17)
HADS	(n=77)
Food diary	(n=17)
Bowel diary	(n=20)
Questionnaires	82.75%
Response rate	
Diaries	18.5%
response rate	_
Table-2: Questic	nnaires used

Table-1: Baseline characteristics of patientsrecruited in the audit.

Table-2: Questionnaires used and responses' returned rate.

Prevalence and severity of constipation

Constipation occurs when bowel movements become difficult or less frequent than usual. The frequency or time between bowel movements ranges widely from person to person. Some people have bowel movements several times a day while others only one to two times a week. Having an infrequent bowel movement (i.e. more than three days) is considered too long $^{(15)}$.

Table-3 shows the summary of median scores of questionnaires used in the study. CCCS score for female and male subjects were respectively 7.5 and 4; PAC-SYM score for female and male subjects were respectively 6 and 3; PAC-QoL score for female and male subjects were respectively 25 and 22; St Martin' score for female and male subjects were respectively 5 and 2.5; Anxiety score for female and male subjects was 7, and Depression score for female and male subjects was 5.

Questionnaires		Scoring	Comments	Score median	
-		range		Female	Male
CCCS	(n=79)	0-30	0= less severe	7.5	4
PAC-SYM	(n=83)	0-480	0= mild (no cut-off score)	6.0	3.0
PAC-QoL	(n=82)	0-112	0= better Quality of Life	25	22
St Marks	(n=75)	0-240	0= perfect continence	5.0	2.5
Anxiety test	(n=77)	0-21	11= breaking point	7	7
Depression test	(n=78)	0-210	11= breaking point	5.0	5.0

Table-3: Summary of median scores of questionnaires used in the study

Perception by patients

Cleveland Clinic Constipation Score, CCCS[©] (n=79)

30-point system questionnaire used to define patients' symptoms suggestive of constipation.

The scoring system consisted on eight variables: frequency of bowel movements, difficulty or painful evacuation, completeness of evacuation, abdominal pain, time

per attempt, type of assistance, number of unsuccessful attempts at evacuation in a 24-h period, and duration of constipation. A total score can range from `0=normal' to '30=severe constipation'. A cut-off score of 15 suggests constipation.

A total of 48 female and 31 male took part in the survey. 96% of female (n=46) and all male participants (n=31) scored under 15 points. 4% of female (n=2) scored 20 points (Fig-1a). The median score for female and male participants were respectively 7.5 (range 0-20) and 4 (range 0-14).



Figure-1a: CCCS symptoms suggestive of constipation. Most patients scored \leq 15. No maximum score achieved.

Most of patients have managed constipation without assistance (n=75); some patients treated their constipation with stimulative laxatives (n=15), and 2 patients have used digital enema (Fig-1b).



Figure-1b: Most patients have managed constipation without assistance.

Patient Assessment of Constipation Symptoms, PAC-SYM[©] (n=83) 48-point system questionnaire used to measure patient's experience of symptoms and their severity in constipation over a 2-week period of time.

The scoring system consisted on 12-item questionnaire divided into abdominal, rectal and stool domains. A total score ranged from '0=absent' to '48=very severe'. No cut-off score has been reported $^{(16)}$.

A total of 51 female and 32 male participants took part in the survey. 94% of female (n=48) and all male participants scored <24 points. 6% of female (n=3) scored 27, 31 and 40 points (Fig-2a). The median scores for female and male subjects were respectively 6 (range 0-40) and 3 (range 0-24).



Figure-2a: PAC-SYM severity of constipation. Most participants scored \leq 24.

A total of 43.4% of patients (n=36) did not require straining to pass bowel movements. However, 56.6% of patients (n=47) required moderate to mild straining, while 7.2% of patients (n=6) had to deal with severe or very severe straining (Fig-2b).



Figure-2b: Straining severity on constipated patients.

Impact on patients' quality of life

Patient Assessment of Constipation Quality of Life, **PAC-QoL**[©] (n=81) 112-point system questionnaire designed to measure the impact that constipation has on patients' daily life during a 2-week period of time. It comprises 28-items grouped into four subscales: physical discomfort, psychosocial discomfort, worries, concerns, and satisfaction. Each question is scored from 0-4, with lower scores indicating a better quality of life (Fig-3). 52 female and 29 male participants completed the survey.

The median scores for female and male subjects were respectively 25 (range 0-88) and 22 (range 0-62). 98% of female (n=51) and 96% of male (n=28) scored \leq 60 points.



Figure-3: PAC-QOL most scores for male and female were \leq 60. No maximum score achieved.

St Marks Incontinence Score[©] (n=75)

24-score system designed to measure patients' perception on bowel control, in order to evaluate the severity of incontinence (gas, fluid, solid). The survey consisted on 7-questions grouped into two subscales. Scores ranged from '0= never' to '24= complete incontinence' (Fig-4). A total of 47 female and 28 male took part in the survey. All male participants scored \leq 7 points. 91% of female participants scored <12 (n=43), and 9% of female scored from 16-20 points (n=4). The median scores for female and male subjects were respectively 5 (range 0-19) and 2.5 (range 0-7).



Figure-4. St Mark's incontinence score. Male scored ≤ 7 , and females scored ≤ 20

Hospital Anxiety (n=76) and Depression (n=77) Scale, HADS[©]

21-score system designed to help doctors to understand how patients felt regarding their condition. Each question on the test scored from 0-3. Scores \geq 11 were considered to be a 'significant case' of psychological morbidity. Scores between 8 to 10 represented 'borderline cases'. Scores \leq 7 were considered 'normal'. The median anxiety scores for female and male subjects was 7, female range 0-18, and male range 0-16 (Fig-5). The median depression scores for female and male subjects was 5, female range 0-18, and male range 0-15 (Fig-6).



Significant Anxiety Scale scores for male and females subjects were respectively 14% and 25%.



Significant Depression Scale scores for male and females subjects were respectively 7.1% and 10.4%.

Food and Drink Diary

Patients completed a Food and Drink Diary (n=17) over a week period of time (on Saturday, Monday and Tuesday⁵), in order to monitor whether they were meeting recommended servings and nutritional intake (Table-4).

Energy daily intake

The average daily energy intake of female participants was 1,636 kcal (range 993 to 2,625), which amounts to 81.8% of the recommended 2,000 kcal. Male participants consumed only an average of 1,721 kcal (range 1,251 to 3,046), which amounts to 68.84% of the recommended 2,500 kcal.

Micronutrients daily intake

Table-5 shows the recommended daily intake of micronutrients for adults (31-50 years).

The recommended daily intake of water is 3.7 L. However, water consumption average was about 1.3 L/day (range 1,339.26 to 1,302.20 L/day). The recommended daily intake of potassium is 4.7 g⁶, however, participants showed a lower intake of 2.4 g (2,374.06 mg) and 2.5 g (2,484.86 mg) for male and female respectively. The recommended daily intake of sodium is 1.5 g⁷, however, participants showed a higher intake of 1.9 g (1,867.06 mg) and 2 g (1,968.64 mg) for male and female respectively. The recommended daily intake of vitamin-D is 10-15 μ g⁸, however, Table-5 shows both, male and female participants in this study having a considerably lower intake of 3.09 μ g and 2.85 μ g respectively.

Daily intake		Male	Female				Male	Female	
Energy	(kcal)	1,721	1,636	_	Water	(L)	1,339.26	1,302.20	
Protein	(g)	262	250		Potassium	(mg)	2,374.06	2,484.86	
	(%)	16	14.5		Sodium	(mg)	1,867.06	1,968.64	
CH	(g)	730	694		Vitamin D	(µg)	0003.09	000.2.85	
	(%)	44.6	40.3		Table-5 : Median value of patients' daily intake of micronutrients and water.				
Fat	(g)	656	625						
	(%)	40.1	36.3						
Fibre	(g)	31	28.5						
	(%)	1.9	1.7						
Fruit	(g)	142	133						
Vegetable	(g)	195	194						
Meat	(g)	180	164						
Bread, white	(g)	49	52.75						
Bread, brown	(g)	23	26						

Table-4: Median value of patients' daily intake of nutrients.

⁵ Appendix-4 Raw Data (available on request).

⁶ Institute of Medicine. Dietary reference intakes for potassium [Internet]. Available at: http://iom.nationalacademies.org/~/media/Files/Activity %20Files/Nutrition/DRIs/DRI_Electrolytes_Water.pdf?la=en

⁷ Institute of Medicine. Dietary reference intakes for sodium [Internet]. Available at: http://iom.nationalacademies.org/~/media/Files/Activity %20Files/Nutrition/DRIs/DRI_Electrolytes_Water.pdf?la=en

⁸ Institute of Medicine. Dietary reference intakes for calcium and vitamin-D [Internet]. Available at: http://iom.nationalacademies.org/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/calciumvitd_lg.jpg

Bowel movements

Bowel Diary, incorporating the Bristol stool scale (n=17)

Patients kept a Bowel Diary for 7 days, completing information on stool frequency. Consistency was also recorded using the Bristol Stool Scale (BSS), a medical chart designed to classify the form of human faeces into seven categories. Type-1 stool has spent the longest time in the colon and type-7 has spent the least. Stools at the lumpy end of the scale are hard to pass and often require a lot of straining (stools type-1 and type-2 are indicative of constipation). Stools at the loose or liquid end of the spectrum can be too easy to pass, and the need to pass them is rather urgent (stools type-7 are indicative of diarrhoea). The ideal stools are types-3 and 4, especially type-4, as they are most likely to glide out effortlessly.

One patient recorded stool type-1 (hard, abrasive and painful to pass), typical for acute dysbiosis ⁽¹⁷⁾, indicating that this patient experienced severe constipation. Four patients recorded type-2 stools (extreme straining, stays in colon for several weeks), typical for constipation ⁽¹³⁾. Nine patients recorded type-3 stool, likely of IBS (typical for latent constipation, however, transit time is faster) ⁽¹³⁾. Two participants recorded type-4 stools, which are classified as normal ⁽¹³⁾. Finally, one participant recorded watery, non-solid stools type-7, which are indicative of diarrhoea (Fig-7).



Figure-7: Bristol Stool Scale shows that 5 participants experienced constipation (stool types 1 and 2), and 9 experienced latent constipation (stool type 3)

Other parameters

International Physical Activity Questionnaire – Short Form, IPAQ-SF[©] (n=88)

This questionnaire assessed the physical activity (vigorous, moderate, walking and sitting) undertaken by patients across a comprehensive set of domains including: leisure time, domestic and gardening activities, work-related activity and transport-related physical activity. Our data shows that 39 out of 88 patients (44.3%) carry out vigorous exercise (i.e. stair machine, jogging, running, tennis or badminton); 41 out of 88 patients (46.5%) carry out moderate exercise (i.e. fast walking, aerobic class, strength training, or swimming); however, 75 out of 88 participants

(85%) walked a median of 1h per day (range 0.08-6h). Finally, 82 out of 88 participants (93.2%) spent a median of 6h/day sitting (range 1-14h).

Discussion

This clinical audit assessed the characteristics of constipation in 100 patients with Multiple Sclerosis (pwMS) using the Neurology services at the Royal London Hospital. No previous audits of bowel function have been performed on this patient population.

Constipation is often regarded as the infrequency of bowel movements when in fact involves several symptoms and factors that vary in intensity from one patient to another. Therefore an individualized approach to constipation would be always recommended since a combination of factors such as poor diet, reduced or lack of physical activity and depression may affect the digestive system of pwMS. Medications and supplements may also contribute to constipation, considerably affecting patients' quality of life.

Patients' perception on constipation was recorded by the CCCS test. A cut-off score ≥ 15 suggested of constipation, however most participants (96%) scored ≤ 15 points in a scale of 0-30. These findings sharply contrast with studies suggesting that in the UK constipation affects between 3% and 15% of the population ⁽¹⁸⁾. Although this result does not translate into constipation, it does suggest that the group still experienced several degrees on symptoms suggestive of constipation that should be addressed in a further thorough study.

PAC-SYM was used to assess constipation severity on 83 patients. Most participants (96.4%) scored \leq 24, which indicated that constipation symptoms were from moderate to less severe. 43.4% of patients (n=36) did not require straining to pass bowel movements. However, 56.6% of patients (n=47) required moderate to mild straining, while 7.2% of patients (n=6) had to deal with severe or very severe straining. Given these results, there is much scope for improving, lessen and relieve constipation symptoms by providing a 1-2-1 nutritional assessment and sport guidance.

Patients' quality of life questionnaire reflected the effort that patients made in order to improving their life style and coping with challenging situations. 97% of patients scored \leq 60 points indicating that constipation had a low impact on their quality of life. Further analysis would be needed in order to pursue this subject.

Studies suggest that in the UK incontinence affects 1.4% of the general population over 40 years old ⁽¹⁸⁾. Incontinence can dramatically disrupt the lives of individuals who have this debilitating condition. The inability to control the passage of stool can produce embarrassment and fear of such problem limiting daily activities and social life. On a 24-score scale, St Marks' data seemed to indicate that incontinence was a lesser issue among male patients who scored \leq 7 points. 91% of female participants however scored <12, which showed a more considerable concern about this matter. Additionally, 9% of female scored >20 points, indicating some of them have suffered more upsetting incontinence situations. Further analyses needed.

Understandably, people with MS are more anxious about their future and (potential) level of disability ⁽¹⁹⁾. This is a natural response to the uncertainty of the course of MS and requires resource allocation to manage and improve their lives.

The Hospital Anxiety and Depression Scale (HADS) showed that 23% and 25% of female participants had either 'borderline' or 'significant anxiety'. 14% and 18% of male participants also show 'borderline' and 'significant anxiety' respectively. A number of reasons could be underlying the gender difference here, including socioeconomic factors warranting further investigation.

The Physical Activity Test showed that 90.8% of patients carried out vigorous (44.3%) or moderate (46.5%) exercise. However, I have concerns with regards to the kind of exercise patients were undertaken (mostly low-impact). The main reason for muscle wasting is the lack of exercise, however, this may also occur when muscles do not undergo resistance training. The right frequency, intensity, duration and modality of exercise employed as an intervention for a chronic disease, it is fundamental for muscle toning ⁽²⁰⁾. It was also interesting to note that 85% of patients walked a median of 1h per day. Finally, 93.2% of patients spent a median of 6h/day sitting.

Food diary data showed the low daily calorie intake participants consumed: 81.8% of the 2,000 kcal/day recommended for female, and 68% of the 2,500 kcal/day recommended for male. Micronutrients like potassium and vitamin-D recommended intake were also lower than the daily-recommended intake. Sodium was the exception. Water consumption was alarmingly lower than expected, since it totalled 35% (1.3L) of the recommended daily intake of 3.7L. This may be due to pwMS having problems with bladder function (incontinence), who as a result limit their fluid intake

The above data confirms the pressing need to improve nutritional education among pwMS, in order to better patients' nutritional health and quality of life.

The Bowel diary data showed that perception of constipation vary among patients. 52.9% of MS patients (n=9) recorded Type-3 stool, which is similar to what is often reported by people with irritable bowel syndrome (typical for latent constipation). Bowel habits and perception of constipation vary widely among populations. The prevalence of constipation in the UK has been estimated from 8.2% to 52% ⁽²¹⁾. Our audit suggests over 29% of pwMS suffer from constipation indicating the need to improve our services for better bowel function and management in pwMS.

Conclusion

Our findings show constipation is a significant problem among pwMS using the MS services at the RLH. Almost one third of pwMS suffer from constipation indicating this symptom complex is not sufficiently managed in the current setting with no dedicated service available addressing bowel function in pwMS.

This audit should encourage further data collection and analysis to develop a business case for specialised services, for example a multi-disciplinary clinic run jointly by Neurology and Gastroenterology services.

Virtually all the tools used in this audit could be incorporated in clinical practice, for example as an add-on to the questionnaires collected by the UK MS Society's MS Register. There is ample scope for developing a more comprehensive dataset and analysis. Also, future studies should extend to the total population of MS patients at the RLH. Additional anthropometric data (height, weight, BMI) should be included as well as disease duration, the degree of disability, ethnicity, and religion, to enable creation of an individualised service and empower patients to self-manage, improve their nutrition and quality of life and avoid therefore acute admissions (due to constipation), leading to saving for the National Health Service.

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References

⁽¹⁾ Mackenzie IS, Morant S V, Bloomfield G a, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2014;85:76-84. doi:10.1136/jnnp-2013-305450.Available from: http://jnnp.bmj.com/content/85/1/76.full

⁽²⁾ Motl RW, Learmonth YC, Pilutti LA, Gappamaier E, Coote S. Top 10 research questions related to physical activity and multiple sclerosis. Res Q Exerc Sport. 2015 Jun;86(2):117-29. doi: 10.1080/02701367.2015.1023099. Epub 2015 Apr 15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25874730

⁽³⁾ McKay KA, Kwan V, Duggan T, Tremlett H. Risk factors associated with the onset of Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: A systematic review. Biomed Res Int. 2015 Jan;817238. Epub 2015 Jan 31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25802867

⁽⁴⁾ Feinstein A, Freeman J, Lo AC. Treatment of progressive MS: what works, what does not, and what is needed. Lancet Neurol. 2015 Feb;14(2):194–207. doi: 10.1016/S1474-4422(14)70231-5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25772898

⁽⁵⁾ Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Multiple Sclerosis 2003; 9: 219-27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12814166

⁽⁶⁾ Hospital episode statistics: Admitted patient care 2013 to 2014. [Internet] 2015 Feb 25. Health and social care information centre. Available from: http://www.hscic.gov.uk/pubs/hes1314

⁽⁷⁾ Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum. 1996 Jun;39(6):681-5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8646957

⁽⁸⁾ Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. Scand J Gastroenterol. 1999 Sep;34(9):870-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10522604

⁽⁹⁾ Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol. 2005 May;40(5):540-51. Available from: http://www.ncbi.nlm.nih.gov/pubmed?term=16036506

⁽¹⁰⁾ Lee P H, Macfarlane D J, Lam T H, Stewart S M. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. Available from: http://www.ijbnpa.org/content/8/1/115

⁽¹¹⁾ Maeda Y, Vaizey CJ, Norton C. St. Mark's incontinence score. Dis Colon Rectum. 2007 Dec;50(12):2252. Epub 2007 Sep 27. No abstract available.

⁽¹²⁾ Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6880820 ⁽¹³⁾ Bristol stool chart [Internet]. Available from: http://static1.1.sqspcdn.com/static/f/1451532/22180508/1363249562587/bristol_s tool_chart.pdf?token=UgocP8xywC1satdykpAkXD%2BPqag%3D

⁽¹⁴⁾ Dietplan-6. Foresoft [Internet]. Available from: http://www.foresoft.co.uk/

⁽¹⁵⁾ What is constipation. Gastroenterology Group of Rochester [Internet]. Available from: http://www.gastrogroupofrochester.com/diagnosis/constipation

⁽¹⁶⁾ Sharma S, Agarwal B. Scoring Systems in Evaluation of Constipation and Obstructed Defecation Syndrome (ODS). JIMSA January-March 2012 Vol. 25 No. 1. Available from: http://medind.nic.in/jav/t12/i1/javt12i1p57.pdf

⁽¹⁷⁾ Frosali S et al. How the intricate interaction among toll-like receptors, microbiota, and intestinal immunity can influence gastrointestinal pathology. Journal of Immunology Research. Volume 2015, Article ID 489821. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4452102/pdf/JIR2015-489821.pdf

⁽¹⁸⁾ Jarret MED, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. British Journal of Surgery 2004; 91: 1559-1569. Available from: http://www3.interscience.wiley.com/cgi-bin/abstract/109630867/ABSTRACT?CRETRY=1&SRETRY=0.

⁽¹⁹⁾ Lebrun C, Cohen M. Depression in Multiple Sclerosis. Rev Neurol (Paris). 2009 Mar;165 Suppl 4:S156-62. doi: 10.1016/S0035-3787(09)72128-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19361681

⁽²⁰⁾ Saxton J. Exercise and Chronic Disease: An evidence-based approach. Available at: http://samples.sainsburysebooks.co.uk/9781135999063_sample_525908.pdf

⁽²¹⁾ Mueller-Lissner S A, Wald A. Constipation in Adults. BMJ Clin Evid. 2010; 2010: 0413. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217654/