

Original Article

GUILLAIN-BARRE SYNDROME, CLINICAL FEATURES AT PRESENTATION AND OUTCOME

Muhammad Azhar Shah, Mutiullah Khan, Azhar Hussain, Muhammad Latif, Ikram Ur Rahim and Zahabia Manzoor

Objective: To evaluate the frequency of clinical features of Guillain-Barre Syndrome at presentation and outcome of disease.

Methods: All patients who presented to accident and emergency department of Akhtar Saeed Trust Hospital Lahore and Farooq hospital Lahore; and were diagnosed to have Guillain-Barre Syndrome (using Brighton criteria for the diagnosis of Guillain-Barre syndrome)¹ were included in the study. A total of 64 patients of Guillain-Barre Syndrome over a period of 3 years were studied. There were 37 male and 27 were female patients.

Results: Patients of adult age group with the age range from 15-73 were included in the study; and the highest incidence was in the age group 55-65 (57%). Regarding the antecedent infection, 40.6% had history of diarrhea and 26.56% had suffered from upper respiratory tract infection in the previous two to four weeks. As regards neurological features, 87.5% had acute flaccid paralysis, 53.12% had cranial nerves involvement, 73.43% had sensory deficits and 62.5% suffered from pain. Regarding autonomic dysfunction, out of 64 patients, 45.31% had tachycardia, 4.68% had bradycardia, 43.7% had paroxysmal hypertension, 17.18% had orthostatic hypotension, 17.18% had urinary bladder dysfunction, and 21.87% had diarrhea/constipation. Electromyography (EMG) was performed on all 64 patients, 3.12% had normal EMG, 43.75% were shown to have demyelinating neuropathy, 21.87% had axonal neuropathy and the results were equivocal in 31.25%. Out of 64 patients, 20.31% needed mechanical ventilation on admission and 25% needed mechanical ventilation during their stay in the hospital. After a follow up of 06 moths, 76.56% could walk independently, 15.62% patients had some disability due to their GBS and walked with some aids, while 7.81% died during their stay in the hospital.

Conclusions: Guillain-Barre Syndrome patients need careful monitoring for respiratory, autonomic and cardiovascular complications and may need ICU management in about 1/3rd of cases.

Keywords: guillain-barre syndrome.

Introduction

Guillain-Barre Syndrome (GBS) was first described by its present name by Georges Charles Guillain and Jean-Alexandre Barre² in 1916. The disease is still diagnosed on the basis of its clinical features supported by laboratory investigations. It is the leading cause of acute muscular paralysis in developing countries. Recently, its increased incidence was associated with zika virus infection.⁶ Its subtypes include acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN) and Miller Fisher Syndrome. Previously studies have been performed to evaluate the subtypes and clinical presentation of GBS and their relationship to prognosis.^{3,4} The presenting clinical features of GBS include acute ascending paralysis, bilateral

facial palsy, diplopia, dysphagia, dysarthria, urinary retention, ophthalmoplegia, tachycardia, bradycardia, paroxysmal hypertension, orthostatic hypotension and shortness of breath on exertion. Early accurate diagnosis of Guillain-Barre Syndrome is important when specific treatment is most effective and patients need specific monitoring for respiratory, autonomic and cardiovascular complications. Brighton criteria for the diagnosis of Guillain-Barre syndrome was developed in 2009/2010 for early case detection, monitoring and treatment. In Pakistan, in most of the secondary patient care hospitals, ICU facilities are not available. So, most of the patients of GBS need to be transferred to tertiary care hospitals for management. Data from public sector hospitals in Pakistan suggests suspected rise in cases of GBS. This study was designed to emphasize the importance of early diagnosis and early referral to tertiary care

Management.

Methods

All patients who presented to Accident and Emergency department of Farooq hospital Lahore and Akhtar Saeed Trust Hospital Lahore with acute paralysis from August 2014 to July 2017 and were diagnosed to have GBS (using Brighton criteria for the diagnosis of Guillain-Barre Syndrome)¹ were included in the study. Complete biochemical profiles were sent to the laboratory immediately which consisted of complete blood counts, blood glucose level, urea, creatinine, serum electrolytes, liver function tests, serum electrolytes, liver function tests. After their transfer to medical wards, cerebrospinal fluid analysis, Electromyography (EMG) and nerve conduction studies (NCS) were performed. MRI of brain and spinal cord was performed to exclude other possible diagnosis. The patients were monitored for respiratory complications by measuring bed side vital capacity (VC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP)⁵. Continuous cardiac and blood pressure monitoring was carried out for autonomic and cardiovascular complications associated with GBS. The patients were commenced on standard treatment of plasmapheresis or intravenous immunoglobulin. Most patients needed 6 to 10 total plasma volumes exchanged over a period of 10 to 14 days. Pain was managed by opiates and gabapentin. Deep vein thrombosis prophylaxis was provided by subcutaneous enoxaparin. Patients developing respiratory or cardiovascular complications were transferred to ICU for further management. Average length of hospital stay was between 1 to 2 months. A pre-designed Pro forma was used to collect the information about gender, age, symptoms of antecedent infection, neurological symptoms, autonomic dysfunction, mechanical ventilation on admission and during hospital stay, length of intensive care (ICU) and hospital stay, and outcome at 6 months. Data was analyzed by using SPSS version 17.

Results

A total of 64 patients of Guillain-Barre Syndrome over a period of 3 years were included in the study. Following were the salient features of the results of study. Gender as detailed in (Fig-1), 37 were male and 27 were female patients with male to female ratio of 1.4 (**Table-1**). Patients of adult age group

who suffered from Guillain-Barre Syndrome were studied and amongst them, majority were middle aged to old patients with the age range from 15-73 and the highest incidence was in the age group 55-65 (57%). Patients of paediatric age group (14 years and less) were not included in the study as they were managed in the paediatric department. As regards neurological symptoms on admission, out of 64 patients, 56 patients (87.5%) had acute flaccid paralysis, 34 patients (53.12%) had cranial nerves involvement, 47 patients (73.43%) had sensory deficits and 40 patients (62.5%) suffered from pain (**Table-2**). Regarding autonomic dysfunction, out of 64 patients, 29 patients (45.31%) had tachycardia, 03 patients (4.68%) had bradycardia, 28 patients (43.7%) had paroxysmal hypertension, 11 patients (17.18%) had orthostatic hypotension, 11 patients (17.18%) had urinary bladder dysfunction, and 14 patients (21.87%) had diarrhea/constipation (**Table-3**). Out of 64 patients, 13 patients (20.31%) needed mechanical ventilation admission and 16 patients (25%) needed mechanical ventilation during their stay in the hospital (**Table 4**). Electromyography was performed on all 64 patients, 02 patients (03.12%) had normal EMG, 28 patients (43.75%) were shown to have demyelinating neuropathy and 14 patients (21.87%) had axonal neuropathy. The results of electromyography were equivocal in 20 patients (31.25%) (**Table 5**).

After a follow up of 06 months, 49 patients (76.56%) could walk independently, 10 patients (15.62%) had some disability due to their GBS and walked with some aids, while 05 patients (7.81%) died during their

Table-1: Age and sex distribution.

	Frequency	Percentage
Gender	Male/female ration	37/27
		1.4%
Age (Years)	(Years)	47(15-73)
Antecedent infection	Diarrhea	25/64
		40.6%
	Upper RTI	17/64
		26.56%

Table-2: Neurological symptoms on admission.

Neurological symptoms on admission	Frequency	Percentage
Acute flaccid paralysis	56/64	87.5%
Cranial nerves involvement	34/64	53.12%
Sensory deficits	47/64	73.43%
Pain	40/64	62.5%

Table-3: Autonomic dysfunction.

Autonomic dysfunction	Frequency	Percentage
Tachycardia	29/64	45.31%
Bradycardia	3/64	04.68%
Paroxysmal hypertension	28/64	43.7%

Orthostatic hypotension	11/64	17.18%
Urinary bladder dysfunction	11/64	17.18%
Diarrhea / constipation	14/64	21.87%

Table-4: Mechanical ventilation.

Mechanical ventilation	Frequency	Percentage
Mechanical ventilation on admission	13/64	20.31%
Mechanical ventilation during the course of disease	16/64	25%

Table-5: Type of neuropathy.

Type of neuropathy	Frequency	Percentage
Normal	02/64	03.12%
Demyelination	28/64	43.75%
Axonal	14/64	21.87%
Equivocal	20/64	31.25%

Table-6: Outcome of six months.

Outcome at 6 months	Frequency	Percentage
Walking independently	49/64	76.56%
Patients with disability	10/64	15.62%
Deaths	05/64	07.81%

Discussion

A prospective cross-sectional and observational study comprising a total of 64 hospitalized patients with diagnosis of Guillain-Barre syndrome was carried out. All patients of Guillain-Barre syndrome irrespective of sex and mode of presentation were included; children below the age of 15 years usually were not included in the study as they were managed by the paediatric department. Frequency of various clinical features of Guillain-Barre Syndrome were noted; type of neuropathy according to EMG was diagnosed and the outcome in terms of discharge from the hospital or mortality was documented. The data derived from the study clearly shows that out of 64 patients studied, 37 were males and the remaining 27 were females. This male predominance is also supported by many international studies^{7,8}, and two other studies on Guillain-Barre syndrome recently carried out in Pakistan.^{3,4}

The incidence of antecedent infection in our study was demonstrable in 67.18% of patients, 40.6% patients had history of diarrhea and 26.56% patients had history of upper respiratory tract infection in the preceding 2 to 4 weeks. The results were comparable to Shafqat et al³ a previous study carried out in Pakistan. These results were in contrast to a few international studies^{9,10} conducted in the past in which most patients reported upper respiratory tract infection as compared to diarrhea

as antecedent infection. The most probable explanation for that is the far more occurrence of acute infective diarrhea in our part of the world. Regarding neurological symptoms at presentation, if we compare results of our study to the results of Fokkeet al,¹² a recently performed study in Netherlands, the frequency of acute flaccid paralysis was comparable, 87.5% versus 82.13%, cranial nerves involvement was more in patients in our study, 53.12% as compared to 36.27%. Sensory deficits were 73.43% as compared to 67.74%, and pain was present in 62.5% of our patients as compared to 54.47% of patients in Fokkeet al.¹² If we compare our study results to Shafqat et al,³ a study performed in Karachi, Pakistan, the acute flaccid paralysis in that study was 100% as compared to 87.5% in our study, cranial nerve involvement was 88% as compared to 53.12% and sensory deficits were present in 38% as compared to 73.43% of patients in our study.

As far as autonomic dysfunction is concerned, 21% of patients in our study had autonomic dysfunction. This prevalence of autonomic dysfunction was slightly more as compared to Anandan et al¹¹ a study performed in 2017 in USA, but was considerably less than Shafqat et al³ a study performed in Pakistan in which autonomic dysfunction was 61%.

In our study, 20.31% of patients needed mechanical ventilation on admission and 25% needed the same during their stay in the hospital. Over all 45.31% patients of Guillain-Barre Syndrome needed mechanical ventilation during their course of disease, which were comparable to 55% of patients who needed mechanical ventilation as reported in Shafqat et al³ in Karachi in 2006; but the percentage of patients who needed mechanical ventilation was higher in both the studies conducted in Pakistan when we compare it to the world wide data of mechanical ventilation support needed for Guillain-Barre Syndrome patients. Even the percentage of patients who needed mechanical ventilation on admission in Pakistan was higher than the rest of the world. Most probably, because of poor socioeconomic conditions and the high rate of illiteracy, people seek medical advice late as compared to the developed world. The patients who have milder forms of GBS, most probably don't seek even medical advice. Regarding types of GBS on the basis of electromyography, predominant type was demyelinating (43.7%), followed by axonal (21.87%). The electromyography was normal in 3.12% of patients which does not rule out GBS.^{13,1} The results were equivocal in 31.25% of patients. Although the results of our study were comparable to Shafqat et al³ a study performed in

dominant type of neuropathy on electromyography was axonal (74.43%), and demyelinating type was 22.72%. After a follow up of 06 months, 49 patients (76.56%) could walk independently, 10 patients (15.62%) patients had some disability due to their GBS and walked with some aids, however 05 patients (7.81%) died during their stay in the hospital. The worldwide mortality rate was 2-12%.¹⁵

Conclusion

Most patients of GBS in Pakistan have diarrhea as antecedent infection as compared to respiratory

tract infection in the rest of the world. Acute flaccid paralysis is the commonest presentation of GBS as in the rest of the world. Cranial nerves involvement in Pakistan is higher if we compare it to GBS data worldwide. A high percentage of patients need respiratory support on admission as compared to the world. Patients need mandatory monitoring for complications of the disease during their stay in the hospital. Outcome of the disease is comparable to rest of the world if the patients are managed in a tertiary care hospital.

*Department of Medicine
SIMS/Services Hospital, Lahore*

References

1. Oxford University Press © Fokke, C. et al. Brain 137, 3343 (2014). (Brighton criteria for Guillain-Barré syndrome)
2. Guillain et al., 1916
3. Shafqat S, Khealani BA, Awan F, Abedin SE. Guillain-Barré syndrome in Pakistan: similarity of demyelinating and axonal variants. Eur J Neurol. 2006 Jun;13(6):662-5.
4. Waseem Iqbal, Tahir Mukhtar Sayed, Wasim Wali, Nadeem Ahmed, Aamir Waheed Butt, Zaheer Ahmad Gil. IS Guillain-barré Syndrome Different In Pakistan? Pak Armed Forces Med J 2018; 68 (1):119-24
5. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EFM. Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol. 2001;58(6):893-898.
6. David W Smith, John Mackenzie, Zika virus and Guillain-Barré syndrome: another viral cause to add to the list, The Lancet, Volume 387, Issue 10027, 915 April 2016, Pages 1486-1488
7. Kushnir M; Klein C; Pollak L; Rabey JM, Evolving pattern of Guillain-Barre syndrome in a community hospital in Israel. Acta Neurol Scand. 2008; 117(5):347-50 (ISSN: 1600-0404)
8. Landaverde JM; Danovaro-Holliday MC; Trumbo SP; Pacis-Tirso CL; Ruiz-Matus C Guillain-Barré syndrome in children aged <15 years in Latin America and the Caribbean: baseline rates in the context of the influenza A (H1N1) pandemic. J Infect Dis. 2010; 201(5):746-50 (ISSN: 1537-6613)
9. Jacobs BC, Rothbarth PH, van der Meché FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology. 1998 Oct. 51(4):1110-5.
10. Nelson L, Gormley R, Riddle MS, Tribble DR, Porter CK. The epidemiology of Guillain-Barré Syndrome in U.S. military personnel: a case-control study. BMC Res Notes. 2009 Aug 26. 2:171.
11. Anandan C; Khuder SA; Koffman BM. Prevalence of autonomic dysfunction in hospitalized patients with Guillain-Barré syndrome. Muscle Nerve. 2017; 56(2):331-333 (ISSN: 1097-4598).
12. Christiaan Fokke, Bianca van den Berg, Judith Drenthen, Christa Walgaard, Pieter Antoon van Doorn and Bart Casper Jacobs, Diagnosis of Guillain-Barre´ syndrome and validation of Brighton criteria, Brain 2014; 137; 3343.
13. Albers JW, Kelly JJ Jr. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. Muscle Nerve. 1989 Jun. 12(6):435-51.
14. Van den Bergh PY, Piéret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve. 2004 Apr. 29(4):565-74.
15. Alshekhlee A, Hussain Z, Sultan B, Katirji B. Guillain-Barré syndrome: incidence and mortality rates in US hospitals.

Original Article

PREVALENCE OF CONSTIPATION IN HEALTHY POPULATION, AN OBSERVATIONAL CROSS SECTIONAL STUDY

Asma Sikandar, Syeda Maryam Wasif, Mohsin Zaheer, Sarwat Nazir, Aasia Noor, Nadir Zafar Khan and Ahsan Numan

Objective: To assess the prevalence of constipation in healthy population, study was done at hospital employees and students at PGMI/Lahore General hospital, Lahore.

Methods: This was an observational cross sectional study done in sample population that includes employees and students at PGMI/Lahore general Hospital. All subjects were given set of questions which include 4 constipation related symptoms.

1 - Frequency of bowel movements on a scale of 0-4.

2 - Difficulty or painful evacuation effort on a scale of 0-4.

3 - Assistance required to evacuate.

4 - Duration of symptoms.

Total score was 15 of which 7 was the cut off score, people reporting score 7 and above were considered as constipated while below 7 were healthy non-constipated.

Results: Total 778 healthy individuals (clinically) interviewed. The age range was between 10 year to 60 years old. 66% participants were female whereas 34% were male. According to set of questions 14% participants reported constipation.

Conclusions: Constipation is a common complaint but poorly defined clinical constellation, the definition of constipation is different among studies, where most studies are based on a questionnaire and may result from organic condition. Overall, prevalence of constipation in adults has been estimated as 16% worldwide which is very close to our finding of 14% of healthy population reporting constipation. Demographics of subjects of most of 14% are female and above 55 years of age.

Keywords: constipation, healthy individuals, PGMI/Lahore General Hospital.

Introduction

Constipation is a common complaint but a poorly defined clinical constellation. It is difficult to describe normal bowel function but most people evacuate between three times per day and once every three days.¹ Marginal infrequency beyond this may be attributed to poor diet and frequently responds to bulk laxatives. The definition of constipation is different among studies, where most studies are based on a questionnaire and may result from an organic condition. Overall, the average prevalence of constipation in adults has been estimated as 16% worldwide (varies between 0.7% and 79%); whereas the prevalence of 33.5% was attributed to adults aged 60 to 110 years.² Several prior attempts have been made to study constipation. Drossman and coworkers³ surveyed 789 students and hospital employees and found that 18.5 percent strained at stool more than 25 percent of the time. Moreover, 4.2 percent reported to or fewer bowel movements per week. These figures were slightly higher than Thompson and Heaton⁴ reported in an earlier survey. Although

the survey by Drossman and colleagues queried abdominal pain, distention and incomplete evacuation, it did so in the context of diagnosis of irritable bowel syndrome rather than constipation. Much data have been published regarding psychological abnormalities in patients with constipation. One prior publication included a comparison of symptoms and type of constipation. It has been observed clinically in patients with Parkinsonism that constipation can be present as a part of Parkinson disease. Frequency of non-motor symptoms in Parkinson's disease presenting to tertiary care Centre in Pakistan: an observational, cross-sectional study,⁵ which showed that 56 percent of our population with Parkinson's disease had constipation; however, 31% had constipation before onset of disease.

Methods

This was an observational cross sectional study done in sample population that includes employees and students at PGMI/Lahore general Hospital. All subjects were given set of questions which include 4

- 1- Frequency of bowel movements on a scale of 0 to 4
- 2- Difficulty or painful evacuation effort on a scale of 0-4.
- 3 - Assistance required to evacuate.
- 4 - Duration of symptoms.

Total score was 15 of which 7 was the cut off score, people reporting score 7 and above were considered as constipated while below 7 were healthy non-constipated. Clinically not diagnosed for any chronic disease like Diabetes, Hypertension, ischemic heart disease, cerebrovascular accidents. Both genders were included. Ages ranging from 10 to 60 were included. Marked abdominal pain or significant distention or cramping. Presence of any chronic medical condition that may preclude self-care laxative treatment (paraplegia, colostomy). Patients who presented with advanced severe and unstable disease like Diabetes, Mellitus, Hypertension, Ischemic heart disease). Subjects who presented with symptoms and signs of systemic medical conditions that could give rise to constipation like Hypothyroidism. Patients taking drugs that can cause constipation like opioids e.g. morphine, codeine, anti-cholinergic like atropine, trihexyphenidyl, Tricyclic antidepressants, Calcium channel blockers, anti-Parkinson drugs. Data with name, age, gender, occupational status and dietary habits were asked along designed questionnaire to fulfill all the inclusion and exclusion criteria. Questions regarding symptoms of different diseases that were mentioned in the exclusion criteria were asked. Data is analyzed by SPSS version 21 and is used to measure frequencies of responses per item. It has scoring range 1-6 that's normal, score 7 and above 7 is classified as constipated.

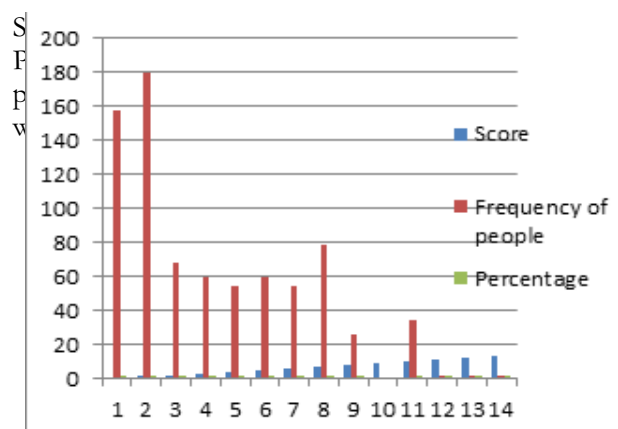
Results

Total 778 healthy individuals (clinically) interviewed. The age range was between 10-60 years old.

Sixty six percent participants were female whereas 34% were male. According to set of questions 14% participants reported constipation.

Discussion

180/778 participants reported minimal intensity and scored 2/14. Pathophysiology and current therapeutic approaches towards Chronic Constipation was studied in a research in 2016 by



X-axis: no of score, **y-score:** number of people.

Excessive straining, a sense of incomplete evacuation, lengthy or failed attempts to defecate, abdominal bloating or pain, hard consistency of stool and use of digital maneuvers for evacuation of stool by Sharma and colleagues.⁶ As participants of current research selected any 2 of 14 constipation criteria given in questionnaire. 76% population reported symptoms of constipation but with normal and healthy severity of it. Healthy severity as scored less than cut off score 7. This showed that prevalence among healthy population is at minimal concern. Leung, Riutta, Kotecha & Rosse in 2011 stated that Chronic Constipation is managed and treated by etiology and evidence-based causes. Dietary fibers, exercise and fluids are the standard advice to treat chronic constipation.⁷ For treatment point of view, such people can be guided and treated easily. And most of them do not consult health practitioners but change diet or follow domestic tips to overcome them. Only 6% research participants reported maximum score and that is 13 and 14. That might have some history, genetic factor or other biological issues, but they did not report any disease or diagnosed severe medical issue. Fourteen percent of healthy population reported symptoms of constipation interpreted as “constipated”, which is close to a study done in western countries, where prevalence rate was stated as between 2%-28%.⁹⁻¹¹ which is supported more closely by a study done in china,¹² which reported that only 14% of general population reported constipation which is exactly the same percentage observed in Pakistani population. Demographics of our study found that most of 14% are female and above 55 year, which is supported

Age, which were cited in 11 and 7 of the studies, respectively. Prevalence rates reported by the selected studies were heterogeneous.⁸ higher prevalence in female gender is also supported by a systemic review done in North America^{9 10} where they found that females were more likely to report FC than males, which was consistent with that in North America, Europe, and Oceania For research concerns, researchers can be interested in finding out that is there any relationship of age and gender in diagnosis, prevalence and severity of constipation.

Conclusion

Constipation is a common complaint but poorly

defined clinical constellation, the definition of constipation is different among studies , where most studies are based on a questionnaire and may result from organic condition. Overall, prevalence of constipation in adults has been estimated as 16% worldwide which is very close to our finding of 14% of healthy population reporting constipation. Demographics of subjects of most of 14% are female and above 55 years of age.

*Department of Neurology
Lahore General Hospital, Lahore
www.esculapio.pk*

References

1. Whitehead WE, Chaussade S, Corazziari E, Kumar D. Report of an international workshop on management of constipation. *Int J Gastroenterol* 1991;4:99-113.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology* 2009;136:741-54.
3. Drossman DA, Sandier RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care. *Gastroenterology* 1982; 83:529-34.
4. Thompson WG, Heaton KW. Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980;79:283-8.
5. Mukhtar S, Imran R, Zaheer M, et al. Frequency of non-motor symptoms in Parkinson's disease presenting to tertiary care centre in Pakistan: an observational, cross-sectional study. *BMJ Open* 2018; 8:e019172. doi:10.1136/bmjopen-2017-019172
6. Division of Gastroenterology and Hepatology, M. C. (2017). NCBI. Retrieved from PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/28185025>
7. Lawrence Leung, T. R. (2011). Chronic Constipation: An Evidence-Based Review. *The Journal of the American Board of Family Medicine*, 436-451.
8. *Journal of Wound, Ostomy and Continence Nursing*, January/February 2014, Volume 41 Number 1, p 70-76
9. Review Epidemiology of constipation in North America: a systematic review. Higgins PD, Johanson J. *Am J Gastroenterol*. 2004 Apr; 99(4):750-9.
10. A review of the literature on gender and age differences in the prevalence and characteristics of constipation in North America. McCrea GL, Miaskowski C, Stotts NA, Macera L, Varma MG, J Pain Symptom Manage. 2009 Apr; 37(4):737-45
11. Prevalence and ramifications of chronic constipation. Harris LA, *Manag Care Interface*. 2005 Aug; 18(8):23-30.
12. *Gastroenterol Res Pract*. 2014; 2014: 532734.