ISSN 2150-5349 (online)

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2020 June 9; 11(2): 8-39

Published by Baishideng Publishing Group Inc

WJGPT

World Journal of Gastrointestinal Pharmacology and Therapeutics

Contents

Irregular Volume 11 Number 2 June 9, 2020

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World Journal of Gastrointestinal Pharmacology and Therapeutics

Volume 11 Number 2 June 9, 2020

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WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, acute infectious gastrointestinal disease, chronic noninfectious inflammatory diseases, pharmacologic therapy for hepato-biliary diseases, drug assessment, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, gastrointestinal motility disorders, pain management in gastrointestinal disease, pharmacologic therapy for pancreatic disorders.

INDEXING/ABSTRACTING

The *WJGPT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

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NAME OF JOURNAL
World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN
ISSN 2150-5349 (online)

LAUNCH DATE
May 6, 2010

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Sin-Hyeog Im, Emanuele Sinagra

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2150-5349/editorialboard.htm

PUBLICATION DATE
June 9, 2020

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Pharmacology and Therapeutics

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World J Gastrointest Pharmacol Ther 2020 June 9; 11(2): 17-24

DOI: 10.4292/wjgpt.v11.i2.17

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Case Control Study

Gastrointestinal symptoms in acromegaly: A case control study

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Author contributions: Poullis A and Hayat J designed the project and reviewed the statistics and the manuscript; Bano G identified the cases and reviewed the manuscript; Inayet N collected the data, carried out the statistical analysis and wrote the manuscript.

Institutional review board statement: The study protocol was approved by the South West-Central Bristol Research Ethics Committee and NHS Health Research Authority United Kingdom.

Informed consent statement: All patients had given informed consent for this study.

Conflict-of-interest statement: The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Data sharing statement: The questionnaire data used to support the findings of this study are available from the corresponding author upon request.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and

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Abstract

BACKGROUND

Acromegaly is a chronic disease caused by a pituitary somatotroph adenoma resulting in excess secretion of growth hormone, which leads to excess secretion of Insulin like growth factor 1 from the liver, causing abnormal soft tissue growth. There is increasing awareness that diseases affecting connective tissue are associated with an increase in functional gastrointestinal symptoms. Data was collected from patients with a confirmed diagnosis of acromegaly to evaluate the intensity, variety and impact of abdominal symptoms in comparison with a control group who were healthy participants recruited from the local fracture clinic.

AIM

To evaluate the frequency type and burden of abdominal symptoms in acromegaly in comparison with a control group.

METHODS

Medical documentation of patients with a diagnosis of acromegaly treated in one tertiary medical centre between 2010 and 2017 has been analysed. Data was collected from patients with confirmed acromegaly, using the Short Form Health Survey (SF36) and Rome IV Diagnostic questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ) and compared to a sex- and age-matched control group, to assess the burden of abdominal symptoms. Microsoft Excel and IBM SPSS v 25 were used for data analysis.

RESULTS

Fifty patients with acromegaly (24 male and 26 females; age range 23-64 years, mean 43) and 200 controls (96 male and 104 females; age range 18-84, mean 42.4) were recruited. 92% (46 out of 50) of patients with acromegaly reported abdominal symptoms and 78% (39 out of 50) had at least one functional gastrointestinal disorder according to the Rome IV diagnostic criteria, compared to 16% of controls (OR > 1, $P < 0.0001$). The most commonly reported symptom

Manuscript source: Invited manuscript

Received: December 31, 2019
Peer-review started: December 31, 2019
First decision: January 19, 2020
Revised: April 25, 2020
Accepted: May 29, 2020
Article in press: May 29, 2020
Published online: June 9, 2020

P-Reviewer: Mari A, Wu KL
S-Editor: Dou Y
L-Editor: A
E-Editor: Qi LL

was constipation (69% acromegaly *vs* 21% of controls OR > 1, $P < 0.0001$, 95%CI: 4.4–15.8). 34 out of 50 (68%) respondents met the criteria for functional constipation according to Rome IV. Upper gastrointestinal disorders were also more prevalent in the acromegaly group. There was no statistically significant difference in the prevalence of biliary and anorectal symptoms between the two groups. Patients in acromegaly group scored lower on the mean scores of the eight parameters of SF36 Quality of Life questionnaire (mean scores 60.04 *vs* 71.23, 95%CI: -13.6829 to -8.6971, OR > 1, $P < 0.001$) as compared to the control group.

CONCLUSION

Upper and lower functional gastrointestinal tract disorders (defined by Rome IV diagnostic criteria) are significantly more prevalent in patients with acromegaly compared with healthy age and sex matched controls in our study. Functional constipation is the most commonly reported problem. Poorer quality of life may in part be attributable to the increased prevalence of abdominal symptoms.

Key words: Functional gastrointestinal disorders; Acromegaly; Constipation; Irritable bowel syndrome; Somatostatin; Pituitary

Core tip: Irritable bowel syndrome is the commonest cause of gastrointestinal symptoms. The aetiology is thought to be multi-factorial but remains incompletely understood. Our group has previously identified that patients with connective tissue disorders have an increased incidence of functional gastrointestinal symptoms. Investigating for these symptoms in patients with acromegaly may give further insight into the pathogenesis of functional disorders and irritable bowel syndrome.

Citation: Inayet N, Hayat J, Bano G, Poullis A. Gastrointestinal symptoms in acromegaly: A case control study. *World J Gastrointest Pharmacol Ther* 2020; 11(2): 17-24
URL: https://www.wjgnet.com/2150-5349/full/v11/i2/17.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v11.i2.17

INTRODUCTION

Acromegaly is caused by a pituitary somatotroph adenoma and characterised by excessive secretion of growth hormone (GH)[1,2]. GH stimulates the liver to produce Insulin like growth factor 1 (IGF-1). In addition to the insulin-like effects, IGF-1 can also regulate cellular DNA synthesis and is an important signalling molecule with regards to cancer cell transformation and proliferation, including mitogenesis and apoptosis inhibition[3].

A variety of complications have been reported in patients with acromegaly including cardiovascular diseases, such as hypertrophic cardiomyopathy, heart failure, hypertension, diabetes mellitus or respiratory disorders, obstructive sleep apnoea[4] as well as increased risk of benign and malignant neoplasms including colon cancer[5].

The organic gastrointestinal pathology associated with acromegaly such as increased risk of colonic cancer and an increased risk of cholelithiasis has been studied in detail[6], however the issue of overall burden of gastrointestinal symptoms, particularly the functional disorders in acromegaly and the gastrointestinal effects of its treatment have not been well studied. We have previously identified how changes in connective tissue in hypermobility (in Marfan and Ehlers Danlos) are associated with an increase in functional gastrointestinal symptoms[7]. The impact of soft tissue changes associated with over secretion of GH and gastrointestinal symptoms has not previously been studied.

Somatostatin analogues used in the treatment of acromegaly are also associated with a wide range of abdominal symptoms. Due to the higher risk of colon cancer, acromegaly patients are offered screening colonoscopy during which standard preparation for colonoscopy is often found inadequate, indicating functional and structural change[5,8,9].

Our aim was to evaluate gastro-intestinal symptoms in a cohort of acromegaly patients. We assessed the frequency, character, severity and burden of abdominal symptoms in patients with acromegaly in comparison with a control group.

MATERIALS AND METHODS

Patients

Medical documentation of patients with acromegaly treated in one medical centre (Department of Endocrinology, St George's Hospital, London) between 2010 and June 2017 have been analysed in order to find the information about their diagnosis, treatment and presence of abdominal symptoms. Treatment information including Somatostatin analogues and other medicines with significant gastrointestinal effects were obtained from patients and controls. Selected patients were then asked to fill out Rome IV Diagnostic questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ) and SF36 questionnaire and were included as cases. Results were compared with sex- and age-matched group of controls.

Controls

Participants in the control group were recruited from people who were being discharged from fracture clinic who were otherwise healthy and did not report any other medical problems. Details of treatment history including drugs affecting the gastrointestinal system were obtained.

Statistical analysis

Microsoft Excel and IBM SPSS v 25 were used to analyse the data. A case-control ratio of 4:1 was used. Fisher's exact test was used to analyse the results of R4DQ and one-tailed Independent sample t test was used to analyse the mean scores of SF36. A *P*-value under 0.05 was considered statistically significant.

Screening protocol

All patients had a confirmed diagnosis of acromegaly and were either post treatment or undergoing treatment.

Ethics

The study protocol was approved by the South West-Central Bristol Research Ethics Committee and NHS Health Research Authority United Kingdom.

RESULTS

Fifty patients with acromegaly (24 male and 26 females; age range 23-64 years, mean 43) and 200 controls (96 male and 104 females; age range 18-84, mean 42.4) were recruited in a 1:4 Case:Control ratio. The mean age at diagnosis of acromegaly was 32.44 years and on average participants had their diagnosis confirmed 11.8 years prior to this study. All patients had trans-sphenoidal surgery and 21 (42%) had pituitary radiotherapy in addition. Thirty-seven (74%) patients were using somatostatin analogues (Table 1).

Ninety-two percent (46 out of 50) of patients with acromegaly reported abdominal symptoms (abdominal pain, diarrhoea or constipation) and 78% (39 out of 50) had at least one functional gastrointestinal disorder (FGID) according to the Rome IV diagnostic criteria, compared to 16% of controls (OR > 1, $P < 0.0001$). All female patients with acromegaly reported suffering from at least some abdominal symptoms as compared to 87% of male patients with acromegaly, however there was no statistically significant gender difference observed in the frequency and intensity of symptoms. The use of medicines (antacids, histamine receptor antagonists, proton pump inhibitors, laxatives) used to alleviate gastrointestinal symptoms was also higher and statistically significant in the acromegaly group (Table 2).

A few patients with acromegaly reported multiple abdominal symptoms and qualified for more than one FGID. The most commonly reported symptom was constipation (68% acromegaly group *vs* 7.5% of controls OR > 1, $P < 0.0001$, 95%CI: 4.4-15.8) followed by abdominal pain (22% acromegaly group *vs* 9.5% of controls OR > 1, $P < 0.0001$, 95%CI: 2.5-9.3). Thirty-four out of 50 (68%) respondents met the criteria for functional constipation according to Rome IV. The prevalence of constipation increased with increasing age and was often associated with bloating. All bowel symptoms showed statistically significant prevalence in the acromegaly group. Some oesophageal and gastroduodenal conditions such as functional heartburn, functional

Table 1 Acromegaly demographic and treatment data

	Controls	Acromegaly patients
n	200	50
M:F	96:104	24:26
Age at diagnosis (mean, yr)	33	32.44
Years since diagnosis (mean, yr)	-	11.8 yr
Transsphenoidal surgery	-	50 (100%)
Pituitary radiotherapy	-	21 (42%)
Somatostatin analogue	-	37 (74%)

dysphagia and functional dyspepsia also showed statistically significant prevalence in acromegaly group. There was no statistically significant difference of prevalence of biliary and anorectal symptoms between the acromegaly group and controls (Table 3).

Acromegaly patients scored lower than controls on the mean scores of all eight parameters measured by the SF36 quality of life index. These parameters include physical functioning levels, role limitations due to physical health, role limitations due to emotional health, energy/fatigue levels, emotional wellbeing, social functioning levels, perception of pain and general health (mean scores 60.04 *vs* 71.23, 95%CI: -13.6829 to -8.6971, OR > 1, $P < 0.001$) (Table 4).

DISCUSSION

Acromegaly is a rare and unique disease associated with abnormal soft tissue growth[4] with a prevalence that is estimated at 40 per million in United Kingdom and an annual incidence rate ranging between 2 and 11 cases per million per year, with an equal distribution between genders[10].

Acromegaly is associated with gastrointestinal complications, such as constipation, higher prevalence of colorectal polyps and cancer[11] and higher prevalence of gallstones in patients treated with Somatostatin analogues[12]. Somatostatin analogues used in the management of acromegaly are also associated with a wide range of abdominal symptoms in addition to the known association with gallstones.

The higher prevalence of lower gastrointestinal symptoms in acromegaly could partly be due to slow intestinal motility. Slow intestinal and colonic transit times have been attributed to both acromegaly and its treatment with Somatostatin analogues. Disease related slow gut motility may be worsened because of treatment with Somatostatin. Resmini *et al*[13] demonstrated that patients with acromegaly have a prolonged small intestinal transit time and a prolonged colon transit time. The small bowel transit time calculated by standardized 10 g lactulose hydrogen breath test showed significantly slower oro-caecal transit in patients than in controls, without significant differences between patients treated with Somatostatin and untreated patients. These data suggest that acromegaly itself may cause motility alteration. However Thomas *et al*[14] performed radiological tests to investigate colonic transit and found an increased transit time of colon (66% longer) in patients with acromegaly compared with controls, and it was even more increased during octreotide treatment. This may predispose to small intestinal bacterial overgrowth, which in turn can cause symptoms[13]. Autonomic intestinal impairment due to vagal hypertonia, similar to that demonstrated previously in the cardiovascular system, has been proposed as a pathogenic mechanism[15]. Another proposed pathogenic mechanism could be related to hormonal imbalance which can be influenced by the complex interaction between GH and ghrelin, as shown by Arosio *et al*[16].These gut motility disturbances in acromegaly increase circulating levels of IGF-1, which is a known mitogen[17] that may stimulate the proliferation of intestinal epithelial cells by autocrine and paracrine actions[11].

Our study has also showed a higher prevalence of upper gastrointestinal symptoms (functional heartburn, functional dysphagia and functional dyspepsia) in the acromegaly group. Sisman *et al*[18] showed that the prevalence of gastritis, duodenitis, peptic ulcers or intestinal metaplasia were higher in patients with acromegaly than in healthy subjects; while the prevalence of hiatal hernia was lower. Ilhan *et al*[19] demonstrated oesophageal dysmotility manifesting as profound reduction in the amplitude and duration of lower oesophageal sphincter relaxation even in acromegaly patients without any significant gastrointestinal symptoms. George *et al*[20] described a rare case of megaduodenum without any distal obstruction in a patient

Table 2 Acromegaly abdominal symptoms and medicine use

		Controls (*n* = 200)	Acromegaly patients (*n* = 50)	*P* value (Fisher's exact test)
Gastrointestinal symptoms		32 (16%)	46 (92%)	
	Abdominal pain	19 (9.5%)	11(22%)	0.4905
	Diarrhoea	8 (4%)	4 (8%)	0.2652
	Constipation	15 (7.5%)	34 (68%)	< 0.00001[b]
Medicines				
	Regular use of anti-secretory (PPI/H2RA)/antacids	11 (6.5%)	31 (62%)	< 0.00001[b]
	Regular use of laxatives	6 (3%)	46 (92%)	< 0.00001[b]
	Regular use of opioid analgesics	11 (6.5%)	2 (4%)	Not statistically significant
	Somatostatin analogues	-	37 (74%)	

[b]*P* < 0.01, statistically significant. PPI: Proton pump inhibitor; H2RA: Histamine H2 receptor antagonists.

with acromegaly. Somatostatin analogues inhibitory effect on gut motility, particularly antral contractility may also produce or worsen symptoms in patients with delayed gastric emptying[21].

Despite our study not showing any statistically significant difference in the prevalence of biliary symptoms in the two groups, other studies have shown an increased risk of gall stones in acromegaly[22-24]. The increased risk of faecal anaerobic bacteria overgrowth associated with slow gut transit times, with the additional increased risk of impairment of bile acid metabolism may be responsible in part for gallstone development[14]. Ultrasound studies have found increased gall bladder volume in both fasting and postprandial states in acromegaly. These are associated with profound suppression of released cholecystokinin, which is associated with Somatostatin administration. The incomplete gall bladder emptying may be the reason for higher incidence of gall bladder calculi in patients with acromegaly treated with Somatostatin[12].

This study is the first study in our knowledge that looks into the prevalence of various abdominal symptoms in acromegaly. The burden of non-organic gastrointestinal symptoms, particularly the functional disorders in acromegaly and the gastrointestinal effects of its treatment have not been well studied. This study, along with our previous studies on Marfan and Ehlers Danlos[7] gives insight into the possible link between connective tissue abnormalities and irritable bowel syndrome (IBS). IBS is the commonest final diagnosis in patients presenting with gastrointestinal symptoms. The aetiology is multifactorial. This study gives further evidence to the suggestion that connective tissue abnormalities may be the underlying pathology in some individuals with IBS.

The strengths of this study are that for a very rare condition this is a large patient cohort being looked after in one tertiary hospital, with a large control group for comparison. A weakness of this study is that cases were not clinically reviewed to ensure that symptoms had been fully investigated to ensure that the symptom complex was truly functional. Also, it was not possible to analyse for disease duration prior to diagnosis, treatment administered historically, on-going treatment and time since diagnosis were not possible.

The presence of FGIDs affecting both upper and lower gastrointestinal tract in patients with acromegaly is substantially higher than the controls in our study. The lower mean scores on quality of life indicators in the acromegaly group reflect the overall burden of disease on quality of life. The high prevalence of abdominal symptoms may in part explain this. This is likely to be multifactorial and factors such as delayed small intestinal and colonic transit times, treatment with Somatostatin analogues, increased bowel length may all play a part in this. A larger follow up international multi-centre study on the presence of abdominal symptoms in acromegaly and future clinical research focussing on the association of abdominal symptoms with connective tissue abnormalities may further help our understanding of IBS and other FGIDs.

Table 3 Gastrointestinal symptoms in acromegaly patients compared with controls

		Controls, *n* = 200 (%)	Acromegaly patients, *n* = 50 (%)	*P* value (Fisher's exact test)
Oesophageal disorders				
	Functional chest pain	2 (1%)	3 (6%)	0.0561
	Functional heartburn	22 (11%)	15 (30%)	0.0016[b]
	Globus	2 (1%)	2 (4%)	0.1796
	Functional dysphagia	4 (2%)	6 (12%)	0.0053[b]
Gastroduodenal disorders				
	Functional dyspepsia	14 (7%)	12 (24%)	0.0013[b]
	Belching disorders	8 (4%)	5 (10%)	0.1441
	Nausea and vomiting disorders	2 (1%)	2 (4%)	0.1796
	Rumination syndrome	2 (1%)	1 (2%)	0.4895
Bowel disorders				
	Irritable bowel syndrome	12 (6%)	10 (20%)	0.0041[b]
	Functional constipation	22 (11%)	34 (68%)	0.0006[b]
	Functional diarrhoea	10 (5%)	9 (18%)	0.0048[b]
	Functional abdominal bloating/distension	12 (6%)	11 (22%)	0.0015[b]
	Unspecified functional bowel disorder	44 (22%)	25 (50%)	0.0002[b]
Centrally mediated Abdominal pain syndrome		6 (3%)	4 (8%)	0.1165
Functional Biliary pain		1 (0.5%)	3 (6%)	0.0261[a]
Anorectal disorders				
	Faecal incontinence	1 (0.5%)	2 (4%)	0.1028
	Functional anorectal pain	2 (1%)	4 (8%)	0.0157[a]

[a]$P < 0.05$,
[b]$P < 0.01$, statistically significant.

Table 4 Quality of life scores in acromegaly patients

	Controls (mean scores)	Acromegaly (mean scores)	Independent sample *t* test
Physical functioning	100.0	80.0	0.80516
Role limitations due to physical health	100.0	50.0	0.001053[b]
Role limitations due to emotional problems	100.0	100.0	1
Level of energy/fatigue	95.0	45.0	0.001053[b]
Emotional wellbeing	100.0	68.0	0.002175[b]
Social functioning	87.5	50.0	< 0.000076[b]
Pain	77.5	67.5	0.1732
General health	100	30.0	< 0.0001[b]

[b]$P < 0.01$, statistically significant.

ARTICLE HIGHLIGHTS

Research background

Acromegaly results from an excess of growth hormone, which leads to excess secretion of Insulin like growth factor 1 from the liver, causing abnormal soft tissue growth. This is associated with an increase in a number of organic diseases. There is increasing awareness that diseases affecting connective tissue are associated with an increase in functional gastrointestinal symptoms. We are not aware of any other study that has looked into the burden of abdominal symptoms in acromegaly and the impact they have on patient's quality of life as a result of this.

Research motivation

This study is part of a larger study that is assessing the role and significance of connective tissue involvement in abdominal symptoms. We have previously described an increase in functional gastrointestinal symptoms in other diseases affecting connective tissue (Marfan and Ehlers Danlos). In this study we evaluate the frequency of abdominal symptoms in patients with acromegaly.

Research objectives

The main objective of this study was to evaluate if patients with acromegaly had more frequent and intense abdominal symptoms, as described by the Rome criteria, than controls and thus, as a result of this had poorer quality of life. Furthermore, other factors such as use of Somatostatin analogues, which in itself can cause abdominal symptoms, had to be taken into account. The next step in our research would be to carry out objective gastrointestinal physiological studies in larger groups of patients and controls to see if the presence of symptoms reflects actual physiological variations across different groups.

Research methods

Patients with acromegaly were identified from a clinical database at one tertiary medical centre (Department of Endocrinology, St George's Hospital, London). Identified patients were then asked to fill out previously validated questionnaires and results were compared with sex- and age-matched group of controls (recruited from fracture clinic who were otherwise healthy and did not report any other medical problems).

Research results

The results of this study showed that the presence of abdominal symptoms in acromegaly is significantly higher than controls. The results also show that the presence of these symptoms has an overall detrimental effect on quality of life or well being of the patient. This study also supports the increasing awareness in the scientific world regarding the association of connective tissue abnormalities and gastrointestinal or abdominal symptoms. It is yet to be seen if gastrointestinal physiological studies in these patients will be reflective of these results.

Research conclusions

The presence of abdominal symptoms is significantly higher in patients with acromegaly compared to controls and this may have a significant impact on their quality of life. Connective tissue abnormalities are associated with abdominal symptoms as has been shown by this study and other studies and may be one of the underlying reasons behind functional gastrointestinal disorders (FGIDs). Other studies have shown similar results in Ehlers-Danlos and Marfan syndromes and abnormalities of connective tissue such as elastin may be common to these disease processes. This needs to be studied further to see if minor variations in gut connective tissue the cause of FGIDs could be.

Research perspectives

Future research in this area will have to be pursued in an international and multicentre study as it is difficult for one centre to recruit a large number of patients in rare diseases. Gastrointestinal physiological studies would help to see if the variance in symptoms is reflected in physiological variance.

ACKNOWLEDGEMENTS

Thank you to the patients and controls who gave up their time to participate in this study.

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