Table 2. Correlations between serum sCD14 level and clinical parameters.

Factor	rho	P-value
Age (years)	−0.082	0.871
Body mass index (kg/m^2)	0.021	0.522
Visceral fat area (cm^2)	0.123	0.354
Subcutaneous fat area (cm^2)	−0.053	0.517
Fasting Blood Sugar (mg/dl)	0.105	0.188
AST (IU/l)	0.136	0.153
ALT (IU/l)	0.214	0.049
C-reactive protein (mg/l)	0.223	0.047
HOMA-IR	0.217	0.052
NAS	0.354	0.004
Steatosis	−0.042	0.492
Inflammation	0.498	<0.001
Ballooning	0.274	0.051
Fibrosis	0.365	<0.001

Numbers represent the mean ± SD. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model for the assessment of insulin resistance; NAS, NAFLD activity score. The correlation between serum sCD14 levels and other parameters is examined by Spearman correlations coefficient.
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inflammation in patients with NAFLD. A previous report showed that serum sCD14 levels in patients with NASH increased with increasing fibrosis stage; however, that report did not evaluate liver inflammation [33]. By contrast, we showed that serum sCD14 levels are strongly correlated with the grade of liver inflammation but not the stage of liver fibrosis. The serum sCD14 levels were also positively correlated with hepatic CD14 expression levels in patients with NAFLD. These results suggest that increased serum sCD14 levels reflect liver inflammation in NAFLD patients. Similarly, previous report showed that circulating microparticles from CD14 positive cells were correlated with severity of liver inflammation in patients with NAFLD [34]. However, we believe that sCD14 is a very convenient tool for evaluation of liver inflammation grade when compared with microparticles.

Table 4. Multiple logistic regression analysis of factors associated with grade 2–3 liver inflammation compared to grade 0–1 liver inflammation in NAFLD patients.

Factor	Odds ratio	95% CI	P value
Age (years)	1.071	0.992–1.149	0.0729
Gender	1.976	0.241–17.49	0.5287
Body mass index (kg/m^2)	1.110	0.881–1.329	0.3987
ALT (IU/l)	0.995	0.938–1.029	0.2756
C-reactive protein (mg/l)	1.395	0.827–2.339	0.2131
sCD14 (ng/dl)	8.853	1.221–63.08	0.0116*

Abbreviations: ALT, alanine aminotransferase; sCD14, soluble CD14.
doi:10.1371/journal.pone.0065211.t004

Several limitations of our study should be discussed. First, we did not conduct liver biopsies in the healthy control group for ethical reasons. Second, some patient selection bias may exist because liver biopsy may have been reserved for patients with NAFLD who were deemed likely to have NASH. Third, using liver biopsy as the 'gold standard' for assessing the accuracy of sCD14 has important limitations associated with sampling errors, as well as intra- and inter-observer variability, which are at least partly linked to the biopsy size [32]. Finally, serum sCD14 levels may increase in other conditions such as cholestasis, biliary atresia, and ischemia reperfusion injury [35–36]. However, these are extremely unusual conditions.

In conclusion, we confirmed that serum sCD14 may be a useful and non-invasive biomarker for diagnosis of NASH and assessing liver inflammation in patients with NAFLD, who are at high risk of progressing to advanced liver fibrosis. Further research, including larger-scale clinical studies or combination of serum sCD14 and other non-invasive biomarkers of NASH such as CK18, are

Table 3. Clinical and serological characteristics of NAFLD patients with mild and severe liver inflammation.

	Grade 0–1 liver inflammation	Grade 2–3 liver inflammation	P value*
Number (n)	43	70	
Age (years)	47.2±13.2	52.3±12.9	0.046
Gender (male; female)	23;20	43;27	0.037
Body mass index (kg/m^2)	27.9±5.3	29.9±5.9	0.042
Visceral fat area (cm^2)	140.7±35.1	149.8±46.2	0.051
Subcutaneous fat area (cm^2)	199.5±44.9	191.9±48.1	0.226
Fasting Blood Sugar (mg/dl)	105.2±13.1	110.2±13.4	0.251
AST (IU/l)	42.3±14.1	43.2±14.3	0.430
ALT (IU/l)	45.5±12.9	57.1±17.6	0.048
C-reactive protein (mg/l)	0.73±0.46	1.18±0.98	0.043
HOMA-IR	3.43±1.33	3.59±1.31	0.431
sCD14 (ng/dl)	25.7±10.5	31.2±11.6	0.009

Numbers represent the mean ± SD. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model for the assessment of insulin resistance. P values correspond to the comparison between grade 0–1 liver inflammation and grade 2–3 liver inflammation in NAFLD patients using the Student's t-test for continuous factors.
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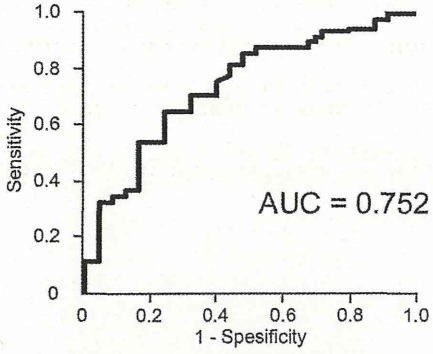

Inflammaroty grade	Cut off value	Se (%)	Sp (%)	PPV (%)	NPV (%)
Grade ≧ 2	29.5 (ng/dl)	78.2	72.4	79.6	62.9

Figure 2. Serum sCD14 levels for diagnosis of the grade of liver inflammation. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUROC) for discriminating between patients with severe (grade 2–3) or mild (grade 0–1) liver inflammation using serum sCD14 levels in 113 patients are shown. Serum sCD14 levels can diagnose severe liver inflammation in patients with NAFLD with moderate accuracy.
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needed to fully investigate the diagnostic and therapeutic implications of our findings.

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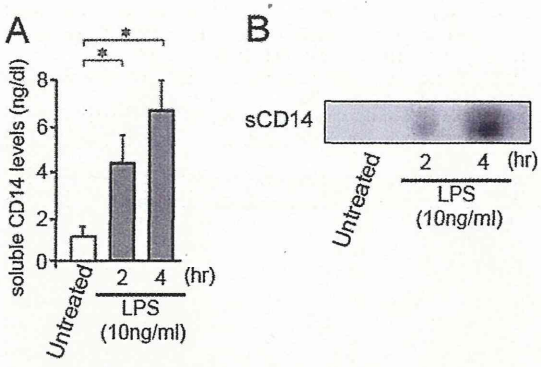

Figure 3. Lipopolysaccharide (LPS) increases sCD14 *in vitro*. sCD14 in cell culture medium from sham- and LPS-treated RAW264.7 cells was compared by (A) Western immunoblot analysis and (B) a sandwich enzyme-linked immunosorbent assay. LPS increased sCD14 in cell culture medium from RAW 264.7 cells. The immunoblot is representative of three independent experiments. Results are presented as means ± SD. Statistical significance was determined using ANOVA with Scheffe's multiple testing correction (*p value <0.05).
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Author Contributions

Conceived and designed the experiments: AN YO KI MY. Performed the experiments: YO KI. Analyzed the data: YO KI TK WT YS SK HM SM YN KF HK. Contributed reagents/materials/analysis tools: KW SS. Wrote the paper: AN YO KI MY.

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JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

Improvement of pneumatosis cystoides intestinalis after steroid tapering in a patient with bronchial asthma: a case report

Akiko Ezuka[1], Kenichi Kawana[1], Hajime Nagase[1], Hirokazu Takahashi[2*] and Atsushi Nakajima[2]

Abstract

Introduction: We report the case of a patient who was diagnosed as having pneumatosis cystoides intestinalis while being treated with prednisolone for bronchial asthma. Even before we had experienced a case of this, the relationship between pneumatosis cystoides intestinalis and prednisolone was unclear. In this case, pneumatosis cystoides intestinalis was improved with the reduction of prednisolone, and therefore we thought a direct relationship between pneumatosis cystoides intestinalis and prednisolone might become clear, such as whether it is dose dependent.

Case presentation: A 62-year-old Japanese woman had been treated for bronchial asthma for approximately 40 years. She presented with abdominal distension, and a radiographic examination showed intraperitoneal free gas and intramural gas, suggestive of pneumatosis cystoides intestinalis. However, when her prednisolone dose was decreased from 30mg to 0mg for approximately a year because of improvement in her asthma symptoms, her abdominal symptom resolved, and the frequency of her bowel movements returned to normal.

Conclusion: Amelioration of pneumatosis cystoides intestinalis was observed with tapering of the prednisolone, suggesting that prednisolone may have been involved in the pathogenesis of pneumatosis cystoides intestinalis in this patient.

Keywords: Asthma, Pneumatosis cystoides intestinalis, Prednisolone

Introduction

Pneumatosis cystoides intestinalis (PCI) is a rare condition in which multiple pneumatocysts develop in the submucosa or subserosa of the colon. PCI was first reported in anatomic dissection by DuVernoi in 1730, and Meyer was the first to use the term in 1925 [1,2]. PCI is characterized by multiple gas-filled cysts in the wall of the large intestine [1], and is an unexpected radiologic finding in many cases [1]. Abdominal pain is the most frequent complaint. We encountered a case of PCI apparently induced by a steroid used for asthma treatment, which resolved with tapering of the steroid.

Case presentation

A 62-year-old Japanese woman was observed for approximately half a year because of upper abdominal pain, however, an upper gastrointestinal endoscopy, fluoroscopic examination and abdominal computed tomography (CT) revealed no abnormal findings. Thereafter, the patient's symptom settled. Four years later, she visited our hospital because of a feeling of fullness in the abdomen and increase in the frequency of bowel movements. An abdominal CT revealed extensive appearance of intramural gas in the colon (Figure 1), particularly in the ascending portion. No abnormality was noted on the surface of the intestinal wall by colonoscopy, except for soft polypoid lesions (Figures 2 and 3). The soft polypoid lesions were 6mm in diameter, on average, with a maximum diameter of 33mm. Pathological examination revealed a cluster of pneumatic cysts in the submucosa and subserosa of the colon, based on which the diagnosis of PCI was made (Figure 4). There was no evidence of inflammation, despite her abdominal symptoms and laboratory findings, including elevated serum C-reactive protein levels and leukocytosis. She has had hypertension, hyperlipidemia, and asthma for decades. She was taking the following routine daily medications:

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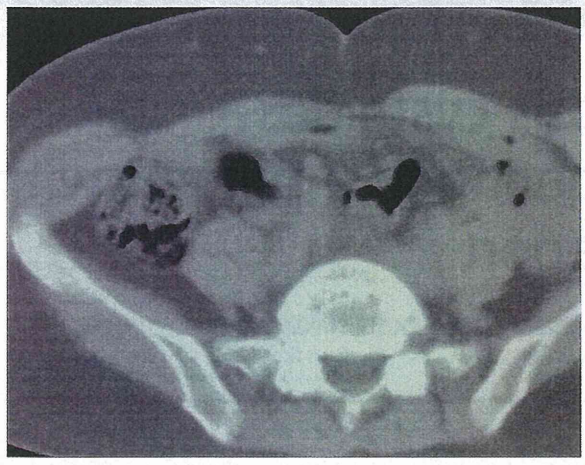

Figure 1 Abdominal computed tomography scan examination showing extensive appearance of intramural gas in the colon.

amlodipine besylate, *Lactobacillus casei*, albumin tannate, and butropium bromide. These medications were continued during the treatment period for bronchial asthma. Prednisolone (PSL) was started at a dose of 30mg/day. During the observation period, the severity of the bronchial asthma symptoms fluctuated. The PSL dose was gradually tapered as the asthma symptoms improved; PSL 30mg was administered each time the asthmatic symptoms increased in severity during the observation period. PSL was the only drug whose dose was modified during the same period.

Discussion

PCI is characterized by the development of multiple submucosal or subserosal pneumatocysts in the submucosa or subserosa of the colon [3-5]. An abdominal X-ray and CT

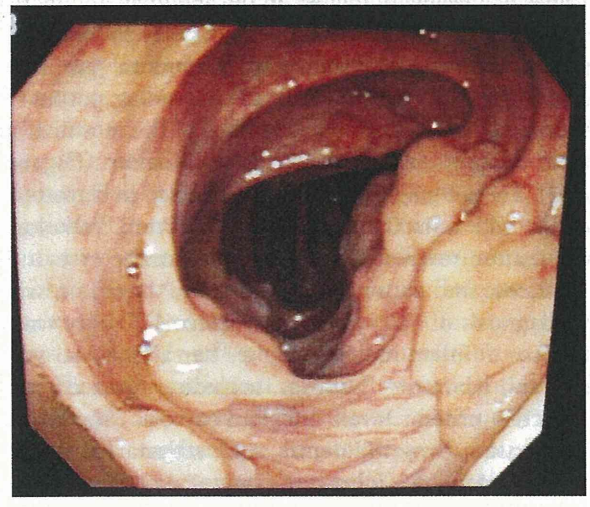

Figure 2 Colonoscopy showing soft polypoid lesions in the digestive tract.

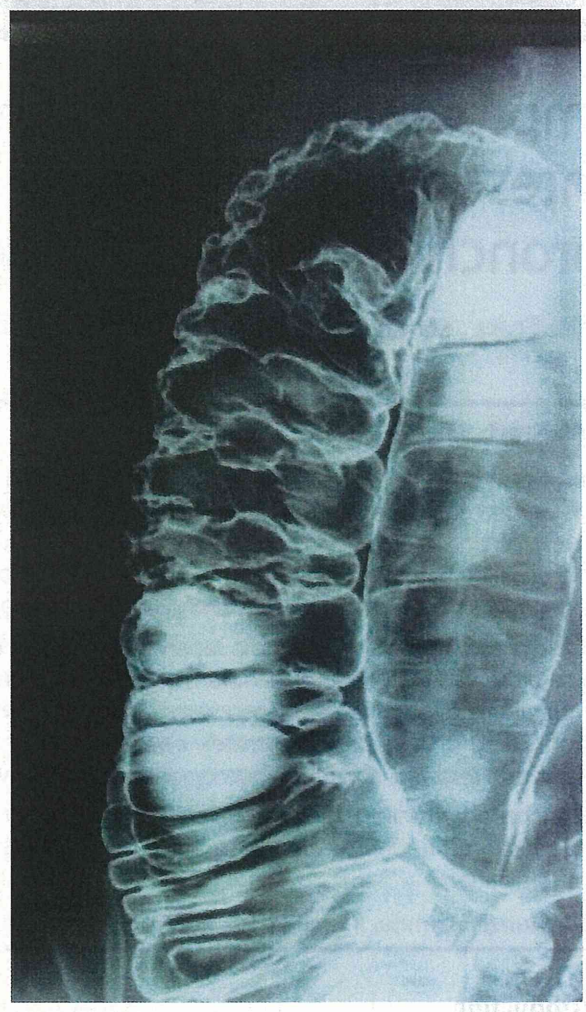

Figure 3 Lower gastrointestinal tract contrast study showing air accumulation in the ascending colon.

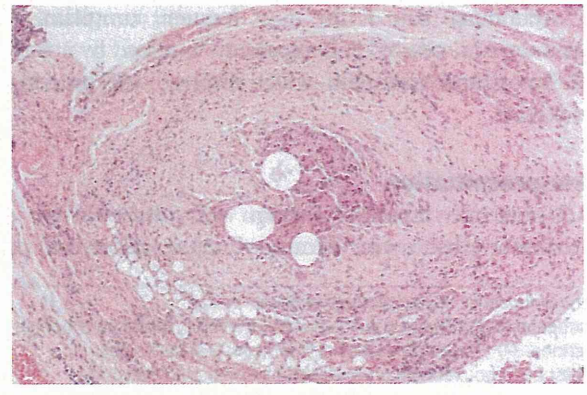

Figure 4 Pathological findings showed pneumatic cysts in the submucosa and subserosa (×50).

demonstrated pneumoperitoneum with massive air accumulation in the intestinal wall, particularly in the colon, leading to the diagnosis of PCI [6]. The etiological mechanisms of PCI are unclear, although PCI has been reported to develop in association with raised intra-abdominal pressure due to ileus surgery, colonoscopy, pulmonary diseases such as chronic bronchitis and emphysema, trichloroethylene exposure, connective tissue disorders, and use of immune-suppressants and alpha-glucosidase inhibitors [3,4]. PSL reduces the number of lymphocytes in the gastrointestinal wall, particularly in the Peyer's patches, impairing the bowel defense barrier system [7], and causes fragility of the intestinal wall, decreased bowel movements, and excessive intraluminal air production [6]. Both bronchial asthma and PSL can cause PCI. Therefore, we could not exclude either as the cause of the PCI in this patient. However, the patient had received PSL for a prolonged period of time, and the possibility of her developing diabetes was high; however, there were no abnormalities in the blood glucose concentration or serum HbA1c, therefore, she did not receive any antidiabetic drug, particularly voglibose. The suspected etiopathogenic mechanism is alveolar air leakage secondary to high airway pressures [8]. Although the very high intrathoracic pressure observed in our patient may have been responsible for such air leakage and contributed to the development of the PCI, gas collections in most cases of PCI associated with pulmonary obstructive diseases occur in the large bowel. It is a secondary finding associated with a wide variety of underlying gastrointestinal or extragastrointestinal diseases, such as autoimmune disease (scleroderma, dermatomyositis), inflammatory disease (inflammatory bowel disease), and infectious diseases (*Clostridium difficile*, human immunodeficiency virus), pulmonary disease (chronic obstructive pulmonary disease, bronchial asthma), drugs (corticosteroids, immunosuppressive therapy), and trauma (blunt abdominal trauma, endoscopy) [1]. In addition, there are also reports on the relationship of pneumomediastinum with PCI. Both pneumomediastinum and PCI can arise as a result of mesenteric ischemia, and therefore occur in patients with ischemic diseases such as acute mesenteric ischemia [9-12].

Conclusions

This patient was diagnosed as having asthma when she was 25-years old, and had been under treatment with PSL for 13 years. She suffered from abdominal pain two or three times per month after having been initiated on treatment with PSL 30mg, however, the abdominal symptom resolved after tapering of PSL. Therefore, development of PCI in the present patient was probably related to the use of PSL 30mg. High-dose PSL and the long-term use of the drug have been reported as risk factors for the development of PCI. She showed dramatic improvement following tapering of the steroid, and is asymptomatic at the present time. At first, we considered whether the onset of PCI depended on the amount of PSL, but the relationship remains unclear. However, because the PCI had improved in parallel with the reduction of the steroid dose, we suggest that the gradual decrease of the steroid dose may have contributed significantly to the improvement of the PCI in our patient. It is noted that PSL is one of the drugs most commonly associated with the development of PCI [1,6]. If a patient being treated with PSL complains of abdominal pain, testing for suspected PCI is needed [1].

Consent

Written informed consent was obtained from the patient for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KK and HN recruited our patient for participation and follow-up at the hospital. AE, HT and AN were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Original Article

Epidemiology and Clinical Experience of Chronic Intestinal Pseudo-Obstruction in Japan: A Nationwide Epidemiologic Survey

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ABSTRACT

Background: We estimated the prevalence and incidence of chronic intestinal pseudo-obstruction (CIPO) in Japan, investigated the patterns of hospital visits among those with CIPO, and examined present knowledge of CIPO among medical professionals.

Methods: A self-administered questionnaire survey was distributed to targeted hospitals throughout Japan, which were selected using stratified random sampling. The questionnaire asked about the number of patients receiving treatment for CIPO, the frequency of their hospital visits, and overall clinical knowledge of CIPO among medical professionals.

Results: CIPO prevalence was estimated to be 1.00 and 0.80 cases per 100 000 males and females, respectively. Incidence was 0.21 and 0.24 cases per 100 000 males and females, respectively. Prevalence and incidence did not significantly differ males and females. Mean age of patients was 63.1 years for males and 59.2 for females. Accurate diagnosis of CIPO sometimes required more than 3 months after initial presentation. Most medical professionals were unaware of or poorly understood CIPO.

Conclusions: We estimated the prevalence and incidence of CIPO in Japan, using data from a nationwide survey. The findings suggest that knowledge of CIPO should be further disseminated so that the disease is not overlooked and is diagnosed without delay.

Key words: chronic intestinal pseudo-obstruction; epidemiology; Japan; prevalence; knowledge

INTRODUCTION

Intestinal pseudo-obstruction is a rare clinical syndrome first reported by Dudley et al,[1] in 1958. Patients present with clinical symptoms of intestinal obstruction but without mechanical obstruction of the intestine. The clinical course is characterized by intermittent/chronic symptoms of intestinal obstruction, such as abdominal pain, bloating, and vomiting. Long-term outcomes are considered poor.[2–9] The syndrome is classified as acute or chronic on the basis of its mode of onset. Among the forms of chronic intestinal pseudo-obstruction (CIPO), primary CIPO occurs in the absence of underlying diseases, is not secondary to drug use, and was formerly referred to as chronic idiopathic intestinal pseudo-obstruction (CIIP).[10] CIPO is an important cause of chronic intestinal failure because affected individuals are often unable to maintain normal body weight or normal oral nutrition. The disease has sometimes attracted the attention of gastroenterologists in Japan and elsewhere.[11]

CIPO is one of the most severe and best described gastrointestinal neuromuscular diseases. Although it is theoretically a diffuse disorder of the alimentary tract, the midgut is usually the worst affected. The condition is characterized by a clinical presentation mimicking small bowel obstruction—with related symptoms and signs—but without demonstrable occlusion of the gut lumen. Sequelae include opioid dependence (for severe abdominal pain) and malnutrition requiring parenteral nutrition, with attendant morbidity and mortality. Although CIPO is uncommon, affected individuals are a major burden for healthcare providers.[3,5]

Little is known of the natural history of this severe condition. Studies have investigated the long-term course of CIPO in children, but few have done so in adults.

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In Italy, Stanghellini studied 59 patients with CIPO: median time from the first subocclusive episode to definitive diagnosis was 8 years (range, 0–47 years). In addition, patients with CIPO had severe limitations in nutritional status at entry and follow-up, as indicated by low body mass index and/or inability to maintain adequate oral intake. After a median of 8 years of follow-up 55.9% of participants had malnutrition, 61.0% were unable to maintain oral feeding, 27.1% required parenteral nutrition, and 8.5% had died.[12]

Clinicians and researchers have proposed diagnostic procedures and algorithms and presented case reports; however, due to the lack of clear, universal diagnostic criteria, no systematic epidemiologic study of CIPO has been conducted.[13] In 2009, the Research Group on Epidemiology, Diagnosis and Treatment of CIIP in Japan proposed diagnostic criteria for CIPO (Table 1),[14] which were validated for clinical use.[15]

Using data from a national epidemiologic survey, we estimated the prevalence and incidence rates of CIPO and identified some of the clinicoepidemiologic characteristics of patients with CIPO in Japan. We also investigated the clinical knowledge and experience of CIPO among medical professionals in Japan.

METHODS

Using stratified random sampling of hospitals in Japan, we conducted a nationwide questionnaire survey in accordance with the procedure used for the nationwide epidemiologic survey of intractable disease in Japan.[16] We sent each participating hospital a questionnaire designed to collect information on CIPO patients and the clinical experience of CIPO among medical professionals.

Selection of hospitals

All departments of gastroenterology, internal medicine, and surgery from all hospitals in Japan are listed in a database compiled by the Welfare and Medical Service Agency of Japan. We categorized these hospitals according to institutional type (university hospital/general hospital) and number of hospital beds. To increase study efficiency, we also selected a group of hospitals that our research network expected would treat at least some patients with CIPO. We separately classified these hospitals as "special hospitals" and surveyed all hospitals in this category. Research partners at Yokohama City University, which has had a long and deep interest in CIPO, were also included in this category. We then randomly selected hospitals from within these categories. The number of surveyed hospitals and their sampling/response rates are presented in Table 2. The sampling rate in general hospitals with 500 or more beds, 400 to 499 beds, and 300 to 399 beds was 52.7%, 52.4%, and 27.7%, respectively. These rates are lower than those outlined in the procedure for the nationwide epidemiologic survey of intractable disease in Japan.

Questionnaire items

First, we asked the heads of hospitals and their departments if they had patients with CIPO and, if so, how many (tabulated by time of diagnosis, i.e., newly diagnosed within the previous year or not). We requested demographic information (age and sex) on those patients. For patients receiving treatment, we next asked the time period from his/her first visit to CIPO diagnosis, the frequency of hospital visits per month, and whether the patient had been seen or treated at other medical facilities before seeking treatment at the present institution. Furthermore, we asked the heads of surveyed medical facilities/departments about their knowledge, information sources, and clinical experience with CIPO.

Survey method

We mailed the self-administered questionnaires to the hospitals. In October 2010, we sent request-for-participation letters, diagnostic criteria, and survey slips to the selected hospitals and requested the number of patients with CIPO treated during the preceding year (from October 1, 2009 through September 30, 2010). The diagnostic criteria used for CIPO (Table 1)[14,15,17,18] were enclosed along with the questionnaires. We sent a series of reminders to nonresponders at the deadline for survey return (end of July 2011). In addition, using direct telephone calls, we repeatedly requested responses from those university hospitals and special hospitals that had not yet responded.

Statistical analyses

We estimated the number of patients treated annually (including newly diagnosed cases) during the period from October 1, 2009 through September 30, 2010, on the assumption that a response from hospitals was independent of the presence/absence of patients and the frequency of their hospital visits.[19] The period prevalence of CIPO was computed based on the estimated number of patients treated (including newly diagnosed cases), while the cumulative incidence of CIPO was computed based on the estimated number of newly diagnosed patients throughout Japan during the given year.[20] The population of Japan in 2009 ($n = 127\,510\,000$)[21] was used to calculate period prevalence and cumulative incidence between October 1, 2009 and September 30, 2010. Due to the stratified sampling design of our study, we adjusted variance estimates for a finite population correction.[22] We conducted statistical analyses using STATA Special Edition, version 11.2 (Stata Corporation, 2009).[23]

Ethical considerations

The Ethics Committee of the Yokohama City University Graduate School of Medicine approved the research protocol before the study began.

Table 1. Definition and diagnostic criteria for chronic intestinal pseudo-obstruction (CIPO)

Definition of CIPO: Chronic bowel obstruction not explained by structural abnormalities

Criteria for CIPO:
(1) Must include all of the following 4 points:
1. Onset of 1 or more symptoms of bowel obstruction at least 6 months before a diagnosis
2. One or both of the following for the previous 12 weeks
   a. Abdominal bloating
   b. Abdominal pain
3. Dilatation and/or air-fluid level of the intestine on abdominal X-ray, echo, and/or computed tomography imaging
4. No evidence of structural disease (on upper and lower gastrointestinal endoscopy, computed tomography, barium enema, and small-bowel follow-through) that could explain the dilatation and/or air-fluid level of the intestine

(2) Important considerations:
1. Congenital disease and onset before age 15 years must be excluded; only adult onset is included
2. Surgical history, except surgery for CIPO, within the 6 months before the diagnosis must be excluded to rule out Ogilvie syndrome
3. CIPO is defined as primary or secondary. Primary CIPO consists of 3 types: myogenic, neurogenic, and idiopathic. Secondary CIPO comprises 2 types: SSc and unclassified
4. Family occurrence may be present
5. Neuropathy, such as problems with urination, may be present
6. Some psychosocial disorder may be present

(Research Group of the Ministry of Health, Labour and Welfare, 2009)

Table 2. Number of patients with chronic intestinal pseudo-obstruction in Japan

	Total no. of hospitals	Surveyed hospitals	Sampling rate (%)	Responding hospitals	Response rate (%)	No. of reported patients	No. of estimated patients (95% CI)
University hospitals	99	99	100.0	75	75.8	35	46 (38–54)
Special hospitals	30	30	100.0	30	100.0	49	49
General hospitals with ≥500 beds	368	194	52.7	63	32.5	15	88 (41–134)
General hospitals with 400–499 beds	349	183	52.4	84	45.9	10	42 (16–67)
General hospitals with 300–399 beds	750	208	27.7	81	38.9	11	102 (18–186)
General hospitals with 200–299 beds	1143	207	18.1	91	44.0	25	314 (34–594)
General hospitals with 100–199 beds	2745	210	7.7	87	41.4	2	63 (0–149)
General hospitals with <100 beds	3346	215	6.4	158	73.5	21	445 (0–930)
Total	8830	1346	15.2	669	49.7	168	1148 (573–1724)

RESULTS

Epidemiology of CIPO

Of the 1346 hospitals initially selected for the survey, 669 responded to the questionnaire (response rate: 49.7%) and identified 168 patients with CIPO (Table 2). On the basis of these reports, we estimated the total number of patients treated throughout Japan during the given year to be 1148 (95% CI, 573–1724; prevalence, 0.900 per 100 000). We estimated that 624 (95% CI, 274–973; prevalence, 1.004 per 100 000) patients were male and 524 (313–735; 0.801 per 100 000) were female. We estimated that 132 (95% CI, 32–233) males and 155 (51–260) females had received a CIPO diagnosis during the previous year (newly diagnosed cases). We estimated the annual incidence of CIPO to be 0.212 per 100 000 for males and 0.237 per 100 000 for females. There was no statistically significant sex difference in the prevalence or incidence of CIPO.

The mean age of patients was 63.1 (95% CI, 56.2–70.0) years for males and 59.2 (54.2–64.2) years for females. The proportion of male patients was estimated to be 54.3%. Regarding age–sex distribution, we observed a bimodal age distribution (peaks at age 40 to 49 years and 70 to 79 years) for male and female patients (Figure).

Diagnosis of CIPO and patient hospital visits

The patterns of hospital visits by CIPO patients are presented in Table 3. The median interval between the first visit to the present hospital and a definitive diagnosis of CIPO was 30, 28, and 47 days for total patients, male patients, and female patients, respectively; 50.5% of patients received a CIPO diagnosis in less than 31 days after the first visit to the present hospital. The proportion who received a CIPO diagnosis later than 90 days after presentation was 28.2%, and the proportion of such patients was significantly larger among females than among males (39.8% vs 18.9%, $P = 0.005$). The median frequency of hospital visits was 1.00 visits/month for total patients, males, and females. Overall, 20% of CIPO patients had visited other medical facilities before receiving a CIPO diagnosis at the present facility. This proportion was significantly larger among females than among males (29.4% vs 12.2%, $P = 0.004$). In addition, 95.0% of male patients and 91.4% of female patients were treated in the hospitals where they received their diagnosis.