Natural History of Chronic Idiopathic Intestinal Pseudo-Obstruction in Adults: A Single Center Study

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Background & Aims: **Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a rare disease characterized by episodes resembling mechanical obstruction in the absence of organic, systemic, or metabolic disorders. Intestinal motor abnormalities have long been identified in CIIP patients. Little is known of the natural history of the disease in adults. This study evaluated the clinical course of CIIP over time.** ***Methods:*** **Fifty-nine consecutive CIIP patients without underlying collagen, vascular diseases, or mitochondrial cytopathies were evaluated between 1985 and 2001. Family history, onset of digestive symptoms, previous surgeries, episodes suggestive of subacute intestinal obstruction, digestive symptoms, body mass index, and feeding habits were recorded. Small bowel manometry was performed by a perfusion technique, and abnormal motor patterns were visually identified. Full-thickness biopsies were available in 11 cases and were processed for immunohistochemical analysis of myogenic and neurogenic components of the gut wall.** ***Results:*** **Patients were prospectively followed up for a median of 4.6 years (range, 1–13 years). Diagnosis was often made several years after symptom onset (median, 8 years). Thus, the majority of patients (88%) underwent useless and potentially dangerous surgeries (mean, 2.96 per patient). Manometry invariably showed abnormal motor patterns. Pathologic findings included neuropathies in all investigated cases and abnormalities of interstitial cells of Cajal in 5 of 11 cases. Long-term outcome was generally poor despite surgical and medical therapies; 4 patients died of disease-related complications, 4 underwent small bowel transplantation, almost one third required long-term home parenteral nutrition, and two thirds had some sort of nutritional limitations.** ***Conclusions:*** **CIIP is a severe, often unrecognized disease characterized by disabling and potentially life-threatening complications over time.**

Chronic intestinal pseudo-obstruction (CIP) is a rare disabling disorder characterized by a severe impairment of gastrointestinal propulsion, mimicking mechanical obstruction in the absence of any lesion occluding the gut lumen.[1–3] Between episodes suggestive of obstruction, patients might be asymptomatic, but they generally experience severe digestive symptoms.[4] CIP is an important cause of chronic intestinal failure because affected individuals are often unable to maintain a normal body weight and a normal oral nutrition. Abnormalities of smooth muscle cells,[2] interstitial cells of Cajal (ICCs),[5] intrinsic (enteric) and extrinsic neural supplies,[2,6] and central nervous system[2] might all, separately or in various combinations,[2,7] play a role in the pathophysiology of CIP. This syndrome can be either a result of a wide variety of systemic, metabolic, or organic diseases or idiopathic in origin (ie, chronic idiopathic intestinal pseudo-obstruction [CIIP]).[2] Although most of CIIP cases in adults are referred to as sporadic, familial forms have been described.[2] Diagnosis of CIP relies on the exclusion of a fixed lumen-occluding lesion by endoscopic and/or radiologic examinations in patients in whom bowel obstruction had been suspected on the basis of typical clinical manifestations and radiologic evidence of air-fluid levels in distended bowel loops.[2,3,8] Small bowel manometry plays a supportive role in defining the diagnosis, because it contributes to differentiation of mechanical from functional obstruction,[9] and it might provide indirect information on underlying derangement of smooth muscle (ie, myogenic CIIP) or enteric nerves (neurogenic CIIP).[2–7,10] Once the diagnosis is established, further tests are needed to identify the presence of potentially curable diseases responsible for secondary forms, as well as for monitoring the patient's condition, particularly the patient's nutritional state and mineral and vitamin deficiencies.

Abbreviations used in this paper: AbnAF, abnormal activity front; AF, activity front; BMI, body mass index; CIIP, chronic idiopathic intestinal pseudo-obstruction; CIP, chronic intestinal pseudo-obstruction; ICCs, interstitial cells of Cajal; MMC, migrating motor complex; NF, neurofilaments; nNOS, neuronal nitric oxide synthase; NO-FED, inability of an adequate meal to abolish MMC; NSE, neuron-specific enolase; PGP 9.5, protein gene product 9.5; SP/TK, substance P/related tachykinins.

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Little is known about the natural history of this severe condition. Some studies have investigated the long-term course of the disease in children who generally present the first manifestations at birth or during the first year of age.[10–13] In infants, the disease appears to have a particularly severe course, with 60%[11]–80%[12] requiring parenteral nutrition and 10%[12]–25%[11] dying before adulthood. Although some deaths are attributable to complications of treatment, including surgery and parenteral nutrition, several predictors of poor outcome have been identified in children including malrotation, short small bowel, urinary tract involvement, histology revealing smooth muscle abnormalities, and small bowel manometric findings suggestive of an underlying myopathic disorder.[10,13] Clinical course, long-term outcome, and prognostic factors of CIIP in adults have not as yet been investigated.

The present study was undertaken to evaluate in CIIP adult patients (1) the clinical course and long-term outcome of the disease and (2) potential prognostic factors (demographic, clinical, and manometric) that predict a poor outcome.

Methods

Inclusion Criteria and Patients

A consecutive series of patients with a presumed diagnosis of CIP, referred to the Laboratory of Functional Gastrointestinal Disorders of the S. Orsola-Malpighi Hospital of the University of Bologna between 1985 and 2001 and investigated by clinical and manometric testing, were considered for the study.

The diagnosis of CIIP was established when all the following criteria were fulfilled: (1) recurrent episodes characterized by abdominal pain and/or distention and possibly associated with nausea and vomiting with symptoms mimicking subacute mechanical intestinal obstruction and prompting hospitalization; (2) lack of mechanical causes of gut lumen occlusion, as detected by endoscopy and/or radiology; (3) radiologic evidence of dilated bowel loops with air-fluid levels obtained during at least one acute exacerbation; (4) absence of recognizable organic, systemic, and metabolic diseases underlying the syndrome of CIP as detected by a complete diagnostic work-up.[2,3] Psychological and psychiatric disorders were assessed by at least one formal psychiatric examination in all patients. A formal assessment of autonomic disorders was performed only in patients with a clinical suspicion of such conditions by means of a standardized battery of tests exploring cardiovascular reflexes (head-up tilt test, Valsalva's maneuver, deep breathing, and sustained handgrip) and heart rate variability.[14]

One hundred four patients (70 women; mean age at entry, 38.4 ± 14.2 years; range, 18–74 years) were evaluated during the study period. Of these, 45 (43.3%) were excluded because they did not fulfill the inclusion criteria (Figure 1). The remaining 59 patients (40 women, 68%; mean age at entry, 39.0 ± 14.2 years; range, 18–67 years) were included in the study and prospectively followed up for a median of 4.6 years (range, 1–13 years). Data from hospital records were used to assess the frequency of pseudo-obstruction episodes and surgical procedures; follow-up records extended for a median of 25 years (range, 2–61 years). The family history was collected and pedigree reconstructed by clinicians trained in gastroenterology and genetics. Only 2 patients had familial forms of CIP and more specifically were classified as familial visceral neuropathy; one has been the subject of detailed analysis.[15]

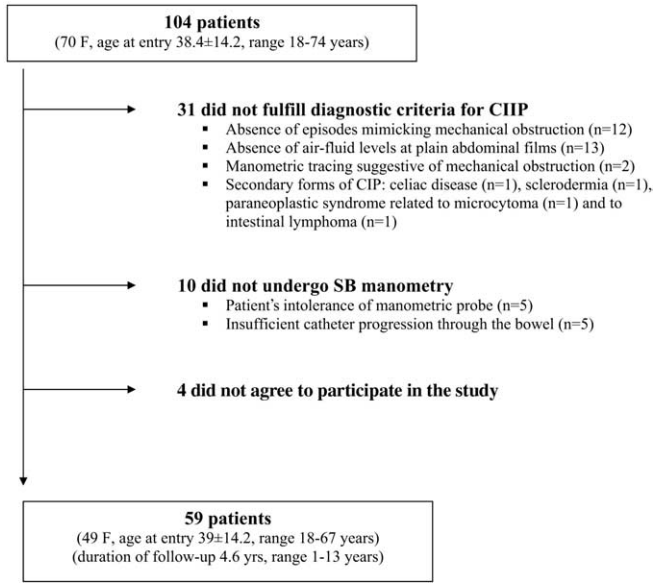

Figure 1. Flowchart summarizing the reasons for exclusion of patients originally referred for suspected intestinal pseudo-obstruction. SB, small bowel.

At entry, each patient underwent a questionnaire on clinical and nutritional parameters and a small bowel manometric test. Furthermore, each patient was prospectively followed up by questionnaire annually or when clinically required. Full-thickness gut tissue specimens were analyzed by immunohistochemical tests whenever available.

Clinical Questionnaire

A detailed questionnaire including 75 questions on relevant issues of health status was completed for each patient during a personal interview at entry. Retrospective information was obtained from interview and medical charts and included family history, age at onset of gastrointestinal symptoms and of episodes suggestive of subacute obstructive episodes, frequency of those episodes, and previous surgical interventions. Prospective information included surgical procedures, episodes suggestive of subacute obstructive episodes, type, severity, and frequency of gastrointestinal symptoms between these episodes as recorded by the Italian version of a previously validated questionnaire that is currently in use in our laboratory,[16] body mass