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Alimentary Tract

Zollinger–Ellison syndrome: Presentation, response to therapy, and outcome

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ABSTRACT

Background: Recent series describing the clinical presentation, response to therapy, and long-term outcome of Zollinger–Ellison syndrome are limited.
Aims: To assess the clinical characteristics and long-term outcome of patients with Zollinger–Ellison syndrome.
Methods: Over a 20-year period, patients with Zollinger–Ellison syndrome were enrolled in a prospective trial evaluating the efficacy of lansoprazole. Following dose stabilization, patients were followed on a 6-monthly basis with interval history, physical examination, endoscopy with gastric biopsies, gastric acid analysis and laboratory studies.
Results: 72 patients (mean age 54 ± 12 years, % male 58%, % Caucasian 69%) were prospectively enrolled. The clinical presentation was stereotypical for Zollinger–Ellison syndrome. Symptoms had been reported for a median of 9 years prior to diagnosis. Cross-sectional abdominal imaging was often negative for demonstrable tumour. All patients had gastric acid hypersecretion controlled with variable doses of lansoprazole (median dose 60 mg/day, range 15–480 mg/day). The median survival from the time of diagnosis was 6.6 years; only two of 19 deaths were due to metastatic gastrinoma.
Conclusions: The clinical presentation of Zollinger–Ellison syndrome was similar to prior reports. Acid hypersecretion was controlled in all patients with variable doses of lansoprazole. Long-term survival was principally related to underlying co-morbidity.

1. Introduction

Zollinger–Ellison syndrome (ZES) is a rare disorder caused by neoplastic production of the hormone gastrin resulting in gastric acid hypersecretion and complicated ulcerative disease of the upper gastrointestinal tract. Since the seminal description of this syndrome in 1955 [1], reports worldwide have better defined the manifestations of disease, approach to tumour staging, surgical management and, in a few studies, long-term outcome has been prospectively assessed [2–6]. Studies characterizing these patients from the United States have been primarily limited to extensive work from the National Institutes of Health (NIH) [6–12]. The purpose of our study, therefore, was to characterise the clinical presentation, response to therapy and long-term outcome of our prospectively collected ZES cohort.

2. Patients and methods

Since 1990, all patients with suspected or confirmed gastric acid hypersecretion and ZES were prospectively identified from hospitalised patients at the University of Alabama Birmingham Hospital, those referred to the gastroenterology outpatient clinic from the surrounding catchment area including the Birmingham Veterans Medical Center and those undergoing gastric acid analysis. We perform approximately 80 gastric acid analyses yearly at our centre. Our referral base includes Alabama, Mississippi, Tennessee, Georgia and the panhandle of Florida. All patients were evaluated prior to study enrolment by one of the principal investigators (BIH, CMW).

The protocol for baseline evaluation and testing has been previously published [13]. Briefly, following informed consent, patients underwent gastric acid analysis if not previously performed. At the same setting, upper endoscopy with gastric antrum and body biopsies was performed as well as routine blood chemistry studies including serum gastrin concentration in the fasting state. If *H. pylori* was found, eradication therapy was given. Evaluation of gastric biopsies was for routine histologic examination including special staining for *H. pylori* infection as well as enterochromaffin-like cell (ECL) density. Since February 2001, serum chromogranin concentration has been routinely measured yearly. Before the gas-

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tric acid analysis done at study entry, proton pump inhibitor (PPI) treatment was suspended for at least 7 days and replaced by high-dose histamine$_2$-receptor antagonist therapy, which in turn was withheld for 36 h. In 7 patients, PPI treatment was not discontinued as the patient either had previously severe symptoms with drug withdrawal or were concerned about recurrent symptoms, and thus the evaluation done at study entry was performed while on the current PPI or histamine$_2$-receptor therapy. Proton pump inhibitor therapy for two of these seven patients was discontinued at a later date in order to perform a baseline gastric acid analysis. There were 12 patients who dropped out of the study at a median of 3.4 years (range: 0.26–10.9 years), primarily due to other comorbidities, relocation, dislike of procedures and, in one case, pregnancy. In these patients, follow-up was obtained for outcome outside of the study protocol and without routine endoscopy, gastric acid analysis or laboratory studies. Secretin stimulation testing was performed to confirm the diagnosis for those patients with gastric acid hypersecretion by gastric acid analysis but with normal or near normal serum gastrin concentration. Cross-sectional abdominal imaging (abdominal computed tomographic (CT) scanning with oral and intravenous contrast and/or octreotide scanning) was often performed at baseline/study entry or at some point during the course of follow-up. The definition of ZES was based upon previously proposed criteria [13].

Following the baseline evaluations, lansoprazole was initiated at 60–90 mg/day orally before the morning meal. Some patients received higher doses at study entry depending upon the prior PPI dose required to control symptoms and the results of gastric acid analysis. Patients were then evaluated every 2 weeks until symptoms resolved and with repeat gastric acid analysis. Dose adjustments were made to maintain basal acid output (BAO) <5 mmol/h, and for patients post gastrectomy, acid secretion of <1 mmol/h was targeted. Following dose titration, patients were then followed every 6 months with intercurrent history and physical examination, gastric acid analysis, upper endoscopy with antrum and body mucosal biopsies, and routine blood analyses. Abdominal imaging was performed for any new abdominal symptoms or signs. Patients with liver metastases at baseline typically underwent follow-up scanning at variable intervals. Hospital records were obtained for all patients admitted outside the UAB health system during the course of the study. The protocol has been approved by our Institutional Review Board since its inception (#F030107005) and is listed on Clincaltrials.gov (NCT00204373).

2.1. Statistical methods

Summary statistics for continuous variables were computed as mean ± standard deviation and range or as median and range/interquartile range where appropriate. Summary statistics for categorical variables were computed as frequencies with percentages. The frequencies and percentages computed were always with respect to the entire cohort of patients, unless otherwise noted. For the survival curve, estimated probabilities of survival were computed and plotted according to the method of Kaplan and Meier. The Mann–Whitney–Wilcoxon test was used to evaluate whether differences in initial doses of stabilization are based on covariates such as smoking status, presence of MEN-1 and *Helicobacter pylori* infection. Spearman rank correlation was used to determine whether differences in initial dose of stabilization were affected by baseline BAO, duration of symptoms from onset to ZES diagnosis, age at study entry and baseline serum gastrin concentration. Fisher's exact test was used for testing the association between antrectomy and relapse. A significance level of 0.05 was used for all tests.

Table 1
Clinical characteristics at study entry.

Variable	No. (%)
Number of subjects	72
Male	42 (58)
Age at study entry	
Mean ± SD	54 ± 11.6
Range	(25–88)
Caucasian	50 (69)
Duration of symptoms to ZES diagnosis (years)	
Median	9
Range	(0–38)
History of ulcer	64 (90)
History of complicated ulcer disease	35 (49)
Bleeding	27
Perforation	0
Both bleeding and perforation	8
Prior ulcer surgery	13 (18)
Existence of MEN-1 syndrome	16 (22)
Prior antisecretory drug use	63 (87.5)
Proton pump inhibitor	60 (83)
H2-receptor antagonist	46 (64)
Tobacco user	36 (50)
Positive *H. pylori*[a]	18 (26)
Serum gastrin (pg/mL)	
Median	520.5
Range	(39–17,491)
Chromogranin A (ng/mL)	
Median	160
Range	(24–830)

[a] By gastric biopsy.

3. Results

Over the 20-year study period, 72 patients were enrolled with ZES. Twenty-two additional patients were considered to have pseudo-ZES as confirmed by gastric acid hypersecretion (BAO > 15 mEq/h) but with negative secretin testing; these patients were enrolled in our treatment trial but are excluded from this analysis. Four additional patients were offered enrolment but two did not qualify, one was considered non-compliant after only 4 days in the study and one died before entry into the study. The characteristics of the cohort at study entry are listed in Table 1. Of the cohort, 56 patients were considered to have sporadic ZES (78%) and 16 (22%) to have multiple endocrine neoplasia syndrome type 1 (MEN-1). Four patients were diagnosed with MEN-1 at a median of 5.8 years after ZES; 11 patients were diagnosed with MEN-1 and ZES within the same 12-month period, and one patient was diagnosed with MEN-1 2 years before the diagnosis of ZES. In the cohort, 22 (31%) patients were African-American and none were Hispanic. Prior complicated ulcer disease was frequent and 13 patients (18%) previously had undergone ulcer surgery. Twenty-four patients (33.3%) had experienced multiple episodes of bleeding and/or perforation. Serum gastrin concentrations were >100 pg/ml in 94%, and >10 x normal in 21%. Of those tested serum chromogranin concentrations were elevated in 95%. As has been previously recognised, patients typically had gastrointestinal symptoms for many years before diagnosis.

3.1. Symptoms

The common reported gastrointestinal symptoms are listed in Table 2. Gastrointestinal bleeding such as haematemesis and melena were present at enrolment in 7.4% of the cohort.

Table 2
Primary gastrointestinal symptoms at study entry.[a]

Variable	No. (%)
Abdominal pain	32 (47.1)
Nausea	31 (45.6)
Heartburn	28 (41.2)
Diarrhea	30 (44.1)
Vomiting	21 (30.9)
Melena	4 (5.9)
Haematemesis	3 (4.4)

[a] Some patients had more than one symptom.

3.2. Endoscopic findings

The endoscopic findings were suggestive of ZES, with the most common endoscopic findings being thickened gastric folds and hyperplastic gastric mucosa (Table 3). Mucosal disease including oesophagitis (14%), ulcer (18%) and duodenal erosions (6%) were infrequently seen at baseline endoscopy likely because the majority of patients were receiving antisecretory therapy prior to baseline endoscopic evaluation.

3.3. Gastric acid secretion

The findings on gastric acid analysis at study entry are given in Table 4. The median BAO was 24.5 mEq/h (interquartile range: (15.1–34.9 mEq/h), and the median MAO was 40.25 mEq/h (interquartile range: (27.5–53.6 mEq/h).

3.4. Evaluation for tumour

Evaluation for the primary site of tumour was performed by abdominal imaging study in 33 patients (46%) at or before study entry; identifiable tumour was found in 7 patients. Four patients with MEN-1 had one or more pancreatic lesions at different locations ranging in size from 3 cm in diameter or less with or without associated duodenal or nodal disease. Liver metastases were found at study entry in 2 patients and subsequently in 3 patients at 2, 7 and 8 years, respectively, after study entry. One patient had liver metastases found at angiography 15 years before study entry and the other patient was found to have a hepatic tumour measuring 5.7 × 6.8 cm at entry. One patient without MEN-1 had a small tumour anterior to the abdominal aorta at study entry.

Table 3
Endoscopic findings at study entry.[a]

Variable	No. (%)
Thickened gastric folds	57 (80.3)
Duodenal ulcer[a]	11 (15.3)
Location	
Duodenal bulb	11 (100)
Postbulbar	1 (9.1)
Number	
One	6 (54.6)
Multiple	5 (45.5)
Oesophagitis	10 (13.9)
Oesophageal stricture	8 (11.1)
Duodenal nodule	7 (9.7)
Barrett's esophagus	5 (6.9)
Fundic gland polyps	4 (5.6)
Duodenal erosion	4 (5.6)
Gastric erosion	2 (2.8)
Jejunal ulcer	2 (2.8)
Oesophageal ulcer	1 (1.4)
Gastric ulcer	1 (1.4)

[a] Complications, location, and number of duodenal ulcers is out of 11. Some patients had more than one endoscopic finding.

Table 4
Baseline gastric acid analysis.

Variable	
No prior acid reducing surgery ($N = 59$)	
BAO (meq/h)	
Median	25.90
Range	(1.5–154.3)
pH	
Median	1.3
Range	(1.1–2.3)
MAO (meq/h)	
Median	41.95
Range	(8.2–108.3)
Prior acid reducing surgery ($N = 13$)	
BAO (meq/h)	
Median	14.30
Range	(5.5–50)
pH	
Median	1.4
Range	(1.1–2.4)
MAO (meq/h)	
Median	23.70
Range	(6.7–56.1)

Three patients had previously undergone resection of pancreatic gastrinoma before enrolment. One underwent resection 3.9 years before study entry. Relapse occurred in this patient at 30 months after resection. Another patient underwent resection 16 years before study entry and relapse occurred in this patient 24 months after resection. The last patient underwent resection 3.25 years before study entry and had no evidence of a relapse. Two patients underwent pancreatic gastrinoma resection after study entry. One underwent resection 5.6 years after study entry and relapse occurred 2 months after resection. The other patient underwent resection 3.5 years after study entry and relapse occurred 4 months after resection. One patient had a duodenal gastrinoma resected 8.6 months after study entry and relapse occurred 1 month post-operatively.

3.5. Treatment

Per protocol, all patients received lansoprazole initially at 60–90 mg per day. Subsequent dose titration was based upon symptoms and results of gastric acid analysis. All patients had control of acid secretion within 3 visits after baseline evaluation. The three most common doses of lansoprazole prescribed for patients were 60 mg/day (25.4%), 120 mg/day (16.2%) and 90 mg/day (12.7%). The doses to control gastric acid secretion ranged from 15 mg/day to 480 mg/day. No differences in initial dose of stabilization were observed based on tobacco use at baseline ($p = 0.82$), MEN-1 status ($p = .45$), duration of symptoms ($p = 0.47$) gastrin level ($p = 0.25$) or BAO ($p = 0.32$). As a patient's age increased, the initial dose for stabilization decreased ($r = -0.28$, $p = 0.018$). Patients without *Helicobacter pylori* infection required a significantly higher dose for stabilization than patients with *H. pylori* infection ($p = 0.01$). Overall, dose adjustments were made in 46 patients (64%) based upon the BAO. Following the first year of stabilization, dose adjustments were made at 19% of the visits; of these changes, dose increases were required in 52% and dose reductions were made in 48%. These adjustments were typically made based upon the results of BAO. At the time of last follow-up, gastric pH and median BAO for the 59 patients without prior acid-reducing surgery were 4.2 (range 2–7) and 1.9 mEq/h (range 0–8 mEq/h), respectively, while those for the 13 patients with

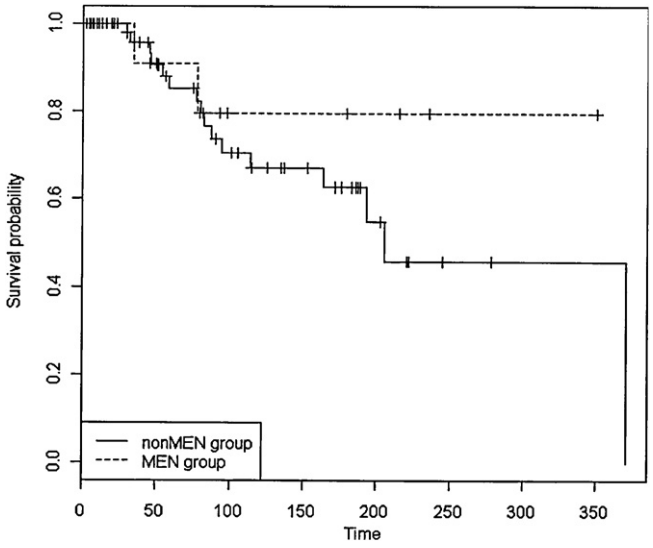

Fig. 1. Comparing the survival of MEN vs. non-MEN patients. The non-MEN group has 16/56 deaths. Median survival time = 6.86 years. The MEN group has 3/16 deaths. Median survival time cannot be estimated as there are only 3 deaths.

prior acid-reducing surgery were 5.1 (range 4.2–7.1) and 0.6 mEq/h (range 0–1.1 mEq/h), respectively.

3.6. Relapse

On follow-up, mucosal relapse was documented in 12 patients (16.7%). The type of relapse included a peptic ulcer in 4.2% (0 gastric, 3 duodenal), reflux oesophagitis in 8 (11.1%) and small bowel perforation in 2 (2.8%). The median time to relapse was 3.9 months (range: 1–36.9 months, interquartile range: 2.2–7.8 months). Patients who had previously undergone antrectomy were much more likely than those without to have a relapse ($p = 0.037$). For patients who had an antrectomy, a jejunal ulcer was most common.

3.7. Follow-up

Long-term follow-up was available to a median of 4.75 years (range 0.15–19.6 years; interquartile range: 1.9–11.1 years). Eleven patients were lost to follow-up at a median of 0.61 years (interquartile range: 0.34–3.17 years) (range 0.15–15 years). The median survival was 6.6 years, and 19 patients died (Fig. 1). The most common cause of death was cardiovascular disease or stroke (9 patients) and cancer (5 patients). The type of cancer included pancreatic cancer, gallbladder cancer and lung cancer. Two patients (ages 67 and 62 years) died apparently due to progressive metastatic gastrinoma ranging from 29 to 46 months from the time of diagnosis. Eight patients died after exiting the study; six of these patients had been excused because of poor health, one was excused due to old age (94 years of age) and distance from UAB, and one was excused because of noncompliance. Of these eight patients, four died of cancer and one died of cardiovascular disease; there was no evidence that any died from metastatic gastrinoma. The non-MEN group had 16/56 deaths with a median survival time of 6.9 years, while the MEN-1 group had 3/16 deaths; the median survival cannot be calculated given the infrequency of death.

4. Discussion

Our large cohort of 72 patients with ZES collected at a single centre with long-term follow-up compliments studies from the NIH and other centres. Our results confirm the stereotypical clinical presentation and long duration of symptoms before diagnosis. Variable-dose PPI therapy was uniformly effective in normalizing gastric acid secretion and abrogating acid-related symptoms. Long-term survival was good and was primarily related to underlying co-morbidity.

The clinical characteristics of our patients both confirm and extend the prospective study of 261 patients from the NIH and literature review of Roy et al. [11]. Several differences can be noted. Our patients were older, less likely Caucasian and symptomatic for a much longer period of time before diagnosis. Abdominal pain was less likely to be reported as an initial symptom by our patients which could reflect recall bias.

Given the efficacy of PPI therapy, which prevents complicated and life-threatening ulcer disease, attention has been placed on tumour identification and surgical removal. While it is generally agreed that surgical therapy is advantageous, which patients exhibit malignant tumours and who will benefit from surgical intervention is less clear. Recent studies suggest that surgical evaluation and tumour removal improves long-term survival [14]. However, such data were generated from non-randomised studies and thus could represent selection bias. In addition, despite the presence of nodal or liver metastasis, long-term survival of patients with gastrinoma can be quite long as the disease assumes an indolent course as noted in some of our patients. Although liver metastases have been repeatedly shown to be a major predictor of survival [6,7] and their presence is associated with large pancreatic tumours [6], even when present, the outcome is variable as metastases may grow very slowly or exhibit no growth in short-term follow-up [15]. The 5-year survival rate for localised disease has been reported to be 60–100% [16]. Surgical series demonstrate that those with Stage I and II disease have approximately 90% survival [17].

Given our prior observations on the high rate of relapse following surgery and the indolent course of many of these tumours, our first approach has been to control gastric acid secretion, manage co-morbidities and not pursue aggressive resection of the primary tumour unless causing symptoms. For those patients with sporadic ZES who are good surgical candidates, surgical evaluation should be entertained. With such an approach, we demonstrate a median survival of over 6 years with most patients dying of other medical comorbidity. Including the patients who dropped out, death from malignant disease was rare, and thus, in our population, our data support a conservative approach in selected patients. In our cohort, cardiovascular disease and cancer were the main causes of death rather than gastrinoma. We can only speculate that our cohort may be different than in other reports perhaps related to risk factors including smoking. One shortfall of our study is that all patients did not undergo extensive radiographic evaluation with somatostatin receptor scintigraphy. These radiographic investigations were performed over two decades, which may reflect why more lesions were not found at initial evaluation by cross-sectional imaging. Regardless, in our small cohort, imaging infrequently identified tumours. This finding might suggest earlier-stage disease or different tumour biology. In addition, an aggressive staging and follow-up for tumour – not employed in the study – did not appear to influence outcome. It is likely some patients with liver metastasis could have been uncovered but the long-term outcome did not seem to be affected. Further studies as to the utility, cost-effectiveness and long-term outcome of routine imaging to assess for metastatic disease are needed. Nevertheless, we recognise a limitation of our study is the fact that patients were not routinely evaluated by an experienced surgical team and that our patients may have self-selected for medical therapy because of associated comorbidity.

Proton pump inhibitor therapy was uniformly effective in controlling gastric acid secretion in our patients. These findings extend short-term studies of other PPIs which have demonstrated normal-

ization of acid secretion and endoscopic remission [18,19]. Relapse of mucosal lesions was rare and generally related to noncompliance, failure to receive the optimal dose of lansoprazole when hospitalised or NSAID use [20]. Long-term lansoprazole therapy even in very high doses was safe and similar to reported outcomes in other long-term studies of patients with GERD [21].

In conclusion, our prospective study confirms the characteristic presentation of ZES. Proton pump inhibitor therapy titrated to acid secretion was a useful approach to defining the ideal dose and was effective in maintaining endoscopic remission. Our study suggests that a medical approach can be associated with long-term survival, and that long-term prognosis in our selected cohort was primarily related to underlying comorbidity.

Disclosure

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Conflict of interest statement

There is no conflict of interest other than C. Mel Wilcox is on the speakers' bureau for TAPP Pharmaceuticals.

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