

Gastric Acid Production, Pancreatic Secretions and Blood Levels of Higher Alcohols in Patients with Fungal-type Dysbiosis of the Gut

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Abstract

Purpose: *Patients with gut dysbioses are clinically difficult to distinguish from those with food intolerance. The variety known as fungal-type is associated with the generation of small amounts of ethanol in the blood. A recent study has shown abnormalities of histidine metabolism. In view of this, gastric function was studied. This also provided data on pancreatic function.*

Design: *Two groups of newly referred patients, with similar symptom profiles, attending two clinicians were studied. Group A (42 patients) had positive ethanol fermentation tests: group B (37 patients) did not. There were 20 healthy control subjects. Levels of higher alcohols, short-chain fatty acids, gastric acid production and pancreatic exocrine secretions were measured and compared statistically.*

Materials and Methods: *Ethanol, higher alcohols and short-chain fatty acids were measured by gas-liquid chromatography. Gastric acid production, emptying time and pancreatic function were measured using a swallowed transducer.*

Results: *A significant number of group A patients had elevated levels of higher alcohols; all of these also showed excess short-chain fatty acids. Group B patients showed similar findings for both; these figures were not statistically significant. However, as compared with group B, group A patients were less likely to show lower levels of gastric acid and/or pancreatic enzyme production and these results were statistically highly significant.*

Conclusions: *As these findings show minimal effects on stomach and duodenum, it is suggested that fungal-type dysbiosis is largely an ileal condition. For these patients, the presence of elevated levels of higher alcohols with a positive ethanol test is a better indicator of disease severity.*

Keywords: *gastric function, hydrochloric acid, pancreatic enzymes, higher alcohols, fungal-type gut dysbiosis.*

INTRODUCTION

Fungal-type dysbiosis (FTD) justifies its separate existence as it responds to a specific treatment programme [1]. A concise and unique clinical description remains difficult, however, as it cannot be separated by history from food intolerance [1]. Patients display all or some of the following: symptoms of irritable bowel (bloating, abdominal pain, increased

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wind and constipation/diarrhoea) and/or catarrhal symptoms and/or psychoneurological symptoms (minimal brain dysfunction).

In most patients there is a remarkable benefit from a diet low in fermentable, yeasty and mould-containing foods, with or without anti-fungal drugs [1, 2]. These dietary measures of necessity cut out or markedly reduce the intake of some foods, leading some to opine that the condition does not exist in its own right, but is at best a variation of food intolerance.

Evidence to the contrary comes from some of the published studies on the condition. The most important are those which demonstrate increased blood ethanol levels after fasting glucose capsule challenge in untreated patients [3]. Patients who have improved after treatment no longer show ethanol increases [1] and ethanol levels are not increased in patients who only have food intolerance [4].

This test has been used clinically as a screening test for FTD and the authors' group has used it as the diagnostic baseline for a number of published studies on the condition. It has not, however, been incorporated into the definition of FTD as some patients who respond to the regime do not produce ethanol. A number of such patients have an excess of urinary β -alanine excretion [5], which again is not present in patients with food intolerance. Other studies have shown that patients with FTD show reduced levels of B vitamins, zinc and magnesium [6], increased gut permeability [4], lowered urinary histidine excretion [7] and a high incidence of elevated breath hydrogen levels [8]. In these studies, there are no significant differences between an FTD group and one with food intolerance, although both have a high incidence of abnormality as compared with healthy controls.

The finding by some of the authors of reduced histidine excretion in patients with classical allergies, food intolerance and FTD [7] led them to consider the biochemical pathways involved. Histidine is an amino acid essential in children and poorly synthesized in adults; humans are thus heavily dependent on dietary intake. Histamine, formed from histidine, which is released in allergic reactions, is largely lost to the body. Thus, a reduction in the urinary loss of histidine is probably a conservation measure. It has been known since the 1930s that hypochlorhydria is common in allergies [9]. The authors' study on histidine excretion demonstrated that it is likely that allergic factors are present in FTD. If allergy causes histidine overuse, and hence conservation via kidney re-absorption, then it was postulated that hypochlorhydria consequent on a reduction in gastric histamine production would probably be a second stage phenomenon and might be a marker of more severe disease. The purpose of this project was to evaluate these mechanisms.

It was impossible to perform a good statistical analysis by merely comparing normal controls with the study group A. Thus, a further group of symptomatic patients, group B, was selected from a concurrent group of patients who had had gastrograms performed but had negative fermentation profiles. As this group had also had both tests, their symptoms were similar. However, in group B two other symptom complexes were noted. The first was belching, feelings of oppression in the epigastrium and reflux; a number of these also tended to vomit. The clinical experience of one of the authors (HCG) associated this quartet with hypochlorhydria. The second complex showed pain below the stomach and a tendency to diarrhoea. In these, one of the authors (HCG) often found pancreatic insufficiency. The patients in groups A and B were matched only in terms of symptomatology: no attempt was made to obtain age and/or sex matching.

METHODS

Patients

Sequential new patients meeting the criteria given in the introduction and attending the two clinical authors (KKE, HCG) were tested for gut fermentation profiles and gastrogram examinations. These constituted group A. At the stage of statistical analysis it became

apparent that a symptomatic group (group B) was required for comparison with the control and FTD groups. Accordingly, a further sequence of patients was incorporated who had had gastrograms examined, but had ethanol-negative fermentation profiles. Beyond the completion of the tests there was no patient involvement and as the investigations carried out for this project were either routine or non-invasive, ethical committee approval was not considered to be required.

Reference ranges were derived from a group of 50 healthy subjects, with no medical complaints and not taking any medication or nutritional supplements.

Laboratory Test Procedures

Gut fermentation profiles were performed by gas-liquid chromatography on patients who abstained from alcohol for 24 hours and from food for 3 hours prior to testing. They were then challenged with a 1 g enteric-coated glucose dose. One hour later, blood was drawn and the following fermentation products were measured: ethanol, methanol, 2-propanol, 1-propanol, 2-methyl-2-propanol, 2-methyl-1-propanol, 2-butanol, 1-butanol, 2-methyl-2-butanol, 2-methyl-1-butanol, 2-ethyl-1-butanol, 2,3-butylene glycol and the short-chain fatty acids acetate, propionate, butyrate, succinate and valerate. As the detailed methodology has been extensively reviewed elsewhere [4, 6, 8], it is not reproduced here.

For the gastrogram, the patients swallowed a plastic-encapsulated transducer, about the size of a small medicine capsule, at least 3 hours after eating. The capsules were made of implantable grade silicone-plastic and contained an induction coil with five associated micro-electrodes. Two electrodes were involved in pH measurements and the other three were involved in the assessment of the efficiency of the pancreatic enzymes. Once a stable resting pH was obtained, two consecutive challenges with sodium bicarbonate solution (1.15 g, in 25 ml of water) were carried out to mimic the small meal situation. The pH curves obtained reflected the efficiency of gastric acid production.

pH monitoring continued as the transducer passed into the duodenum, where pancreatic enzymes began to digest the different thicknesses of protective material covering the other three electrodes. The time taken for each stage was measured and compared with data accumulated from the 50 normal control subjects. The efficiency of the pancreatic enzymes was expressed as a percentage of average normal.

The transducer then passed through the gut and was expelled with the faeces.

Communication with the transducer was by inductive coupling: one coil was outside the body and the other was in the swallowed transducer. The frequency used was 30 kHz and only very low voltages were produced in the transducer. Between the pulses applied to the external matrix, which was contained in an insulated unit placed over the patient, the back electromagnetic field modified by the electrode information was detected, giving information about the position of the transducer, the pH and, later in the test, about the efficiency of the pancreatic enzymes. The gastrogram did not measure amylase.

For most purposes the gastrogram may be used to replace other tests. The Heidelberg capsule uses essentially similar technology, although the signal is a radio signal rather than an electromagnetic one. The Heidelberg capsule is of substantial size and cost, so it consequently must be recovered. Formerly this was done by sieving the stools, but currently it is attached to a thread and is recovered proximally at the end of the test. In practice, this cumbersome technique is seldom used; none is known to be available in the UK. As the technology of the Heidelberg capsule and the gastrogram follows the same basic principle, a comparative trial was not essential [10]. In sampling by endoscopy or intubation, secretion is conventionally stimulated by the instillation of ethanol, supplemented with histamine or pentagstrin when a negative result is obtained. Whilst such invasive procedures tell us something about gastric function, they do not simulate

normal meal situations and do not serve as a model against which the gastrogram may be compared.

The reference values for the authors' laboratory for both test procedures were determined on a group of 20 control subjects (five patients with very specific symptoms, not part of this study, were also studied). The healthy control individuals were free of gut symptoms, had no signs of yeast or fungal infections and had not received antibiotics in the 12 months prior to testing. They were not on any drugs, oral contraceptives, hormonal replacement therapy or nutritional supplements. The same subjects were also used as part of the control group for the gastrogram: none showed hypochlorhydria.

The reference values derived from these subjects for gastric acid production were a resting pH of 1.1–5.8, with pH peaks after the first sodium bicarbonate challenge of 5.5–8.4, the final pH being below 6.0 (the first challenge may only be using up the residual stomach acid). The second challenge should induce some acid production and reference peaks were 6.5–8.4, with a final pH below 5.5. When the first challenge gives a final pH below 2.0, hyperchlorhydria may be present. (Hyperchlorhydria may cause excess acid to be dumped into the duodenum. This may adversely affect pancreatic function as the enzymes work best in neutral to alkaline conditions.) The second challenge may show only a small peak, with the final pH below that of the resting pH and the first challenge final pH. When the first challenge is normal, but the final pH is between 6.0 and 7.0, the results are consistent with mild hypochlorhydria; with a normal resting pH regardless of the first challenge results, a second challenge final pH above 7.0 is also consistent with hypochlorhydria. A resting pH above 5.8 and below 5.0 after the second challenge must be considered normal for the small meal situation. However, stomach acid may be inadequate for larger meals. A resting pH above 5.8 with a final pH above 7.0 indicates marked hypochlorhydria. A resting pH above 6.5 and a final pH above 7.0 for either challenge indicates an achlorhydric patient. With a normal resting pH there may be a peak in the second challenge followed by an obvious acid response and then a secondary pH increase. If this results in a pH of 4.8–6.0 it is deemed due to normal buffering and is not of clinical significance.

For the healthy volunteers, pancreatic enzyme levels ranged from 76 to 141% of the normal mean.

Analysis of the Results

The statistical analyses of the data were performed using Microsoft Excel (Microsoft UK Ltd, Wokingham, Berkshire RG11 5TP, UK) and SPSS (SPSS UK Ltd, Woking, Surrey GU21 1EB, UK).

RESULTS

There were 20 healthy control subjects. Table 1 shows the data for both study groups. Group A was composed of 42 ethanol-positive patients with 37 ethanol-negative patients in group B; thus data were recorded for 99 individuals. The numbers in each group are shown for raised production of higher alcohols and short-chain fatty acids and for patients with hypochlorhydria and diminished pancreatic enzyme production. There were no statistical differences between the two patient groups with regard to production of higher alcohols or short-chain fatty acids. Hypochlorhydria was seen in 17 of 42 (40%) group A patients and 28 of 37 (76%) group B patients. Diminished pancreatic function was found in 13 of 42 group A patients and 27 of 37 group B patients. The chi-squared test demonstrated that these results were statistically highly significant at $p=0.0016$ and $p=0.0005$, respectively.

TABLE 1. Gut fermentation vs. gastric acid production

	<i>n</i>	Gut fermentation profile		Gastrogram	
		Higher alcohols (no. raised)	SCFA (no raised)	Hypochlorhydria	Pancreatic exocrine function $\leq 70\%$
Ethanol-positive group	42	35 (83.3%)	6 (14.3%)	17 (40.5%)	13 (30.9%)
Ethanol-negative group	37	31 (82.6%)	8 (21.1%)	28 (75.7%)	27 (71.1%)
<i>p</i> (chi-squared test)		0.7247	0.5481	0.0016	0.0004

DISCUSSION

Medical science has progressed, but in spite of this there are still big gaps in our knowledge: the biochemistry and microbiology of the small bowel remain very poorly understood and difficult to study. Currently direct access via endoscopy is not merely invasive, but also requires that the patient be purged before intubation, a procedure which removes the very material we need to study. Thus, at present, the only tool for microbiological study is the measurement of fermentation metabolites.

Production by the stomach of hydrochloric acid and of enzymes by the pancreas again present practical difficulties. Whilst direct endoscopic measurement is entirely possible, it is again invasive, with all that that implies; in addition, the preparations undertaken by the patients for the process produce an artificial situation and not a true physiological state. In this study, the utilization of a system involving the recording of electromagnetic signals is both non-invasive and a closer approximation to the situation experienced in daily life by real patients. The authors consider that the gastrogram offers a potentially valuable tool for gastroenterological research.

Attempts over the years have been made to develop theoretical explanations for FTD. However, such theories predict experimental outcomes and, while pathology has always been found, the results have often not been as predicted. Unexpected experimental results make us suspect many of these causal theories.

The purpose of this paper was to study one of the mechanisms of gastric acid production, the secretion of which is dependent on three endogenous chemicals, acetylcholine, released by vagal afferent neurones, gastrin, a hormone for which protein in food is the main release stimulant, and histamine. Histamine is released from mast-like cells in the lamina propria of the stomach, in close proximity to parietal cells. The release of histamine, which is in the H₂ form, may be dependent on gastrin and/or acetylcholine activity. Whichever of these mechanisms from time to time initiates histamine secretion, the entire synthesis is from histidine: if allergic degranulation of cells either in the gut or elsewhere causes total body levels of histidine to fall and urinary reclamation is insufficient [7], then a reduction in gastric histamine should cause hypochlorhydria. The extent to which hypochlorhydria is seen in a study group is potentially a measure of the severity of the allergic component of the disease process. The authors' incorporation of records of pancreatic secretion levels was because the study tool, the gastrogram, enabled these measurements to be made and it seemed wrong to ignore them. The authors had formed no estimate of the extent to which pancreatic function might be affected, although on an empirical basis, earlier workers routinely advised pancreatic supplements for these patients [11, 12].

This study found that 40% in the FTD group (group A) had lowered hydrochloric acid production. Pancreatic deficiency was identified in 30%. The disease-positive control group (group B) was one in which specific abnormalities of hypochlorhydria and/or pancreatic enzyme deficiency were expected as a result of the provisional clinical diagnosis. The

finding of 76% with hypochlorhydria and 70% with pancreatic enzyme deficits was not therefore a surprise. The fact that these results were statistically significantly greater than those found in patients with FTD was equally to be expected from these figures. Group B was an appropriate positive disease control group as the patients shared many major symptoms with group A. They did, however, have extra symptoms: belching, epigastric oppression and reflux, sub-gastric pain and occasional vomiting. That 40% of the FTD group were hypochlorhydric might conceivably be of significance if the authors had been able to study a group of patients solely with FTD symptoms, ethanol negative and not responsive to diet and/or anti-fungals, who were submitted for gastrogram measurement. A repeat of this study using such a group would be of interest. The authors must, however, conclude that, as compared with group B, the FTD patients are less likely to have problems with gastric or exocrine pancreatic function.

Because this study has not found evidence of gastric or duodenal pathology, this perhaps suggests that FTD may primarily be an ileal disease, rather than afflicting the whole of the gut. Furthermore, this work does not support the routine use of pancreatic supplements for these patients, unless supported by positive laboratory testing. It is also concluded that the detection of major excesses of higher alcohols on a gut fermentation profile is a better measurement of the severity of the disease than hypochlorhydria.

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