

Postinfective diarrhoea and bile acid malabsorption

ABSTRACT—Postinfective irritable bowel syndrome with diarrhoea and idiopathic bile acid malabsorption remains an enigma. We examined the records of 84 patients whose $^{75}\text{SeHCAT}$ scans were indicative of bile acid malabsorption (<15% one week retention). Identifiable causes of bile acid malabsorption were: previous ileal surgery (7), Crohn's disease (22), radiation enteritis (13), vagotomy, gastrectomy or cholecystectomy (10) and miscellaneous (3). Sixteen of 29 patients with apparently idiopathic bile acid malabsorption gave a clear history of acute gastroenteritis before the onset of chronic diarrhoea lasting from 0.25–18 years until their positive $^{75}\text{SeHCAT}$ scan. Only four cases of campylobacter, and one each of shigella and salmonella were documented. Extensive investigation failed to detect other possible pathologies. In response to bile acid sequestrants, mean stool frequency fell from 7.2 per day to 2.1 per day ($p < 0.001$). We have observed that postinfective chronic diarrhoea is associated with chronic bile acid malabsorption, which can be successfully treated with bile acid sequestrants such as cholestyramine.

Bile acid malabsorption is a well recognised cause of chronic diarrhoea [1] and may be detected by $^{75}\text{SeHCAT}$ bile acid retention scan [2–5]. This scan is independent of small bowel bacterial overgrowth and utilises the taurine conjugate of a synthetic cholic acid analogue.

The most common identifiable causes of bile acid malabsorption are Crohn's disease [6], terminal ileal resection [5,6], radiation enteritis [7–9], cholecystectomy [10,11], vagotomy [12], and drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) [13]. In a substantial number of patients the cause of bile acid malabsorption is unknown. Bile acid malabsorption in such idiopathic patients has been regarded by some as an epiphenomenon rather than the cause of the diarrhoea [14,15]. We therefore undertook a retrospective study of all patients who underwent a $^{75}\text{SeHCAT}$ scan between 1986 and 1994. It was noted that some positive $^{75}\text{SeHCAT}$ scans in the idiopathic bile acid malabsorbers were associated with a history of severe infective gastroenteritis many years before. In such cases, the diarrhoea could be dated back precisely to the original episode of gastroenteritis.

Method

The $^{75}\text{SeHCAT}$ absorption was assessed by administration of one capsule containing 370 KBq (9.25 μCi) $^{75}\text{SeHCAT}$ after an overnight fast [4,5,16,17]. The baseline value was obtained four hours after this dose with an uncollimated gamma camera for five minutes on the front and back of the abdomen of patients in the recumbent position. Background radiation was also assessed for five minutes before each scan. The scan was repeated after seven days. The hospital medical records of patients with 'positive' scans (ie <15% retention) at one week were studied retrospectively for clinical characteristics and response to bile acid chelators. No patient with a one-week retention of more than 15% has responded to cholestyramine in our experience. This corresponds with the findings of Williams *et al* [17] in their review of 500 patients investigated by $^{75}\text{SeHCAT}$ scans.

Results

A total of 171 patients underwent $^{75}\text{SeHCAT}$ scanning between 1986 and 1994, of whom 90 (52.6%) had a positive scan. Hospital records were available for 84 (93.3%) of these 90 patients, and a recognised cause of bile acid malabsorption was evident in 55 (65.5%) of the 84. The 29 (34.5%) with idiopathic bile acid malabsorption, in whom there was no obvious explanation (Table 1), were further investigated for chronic diarrhoea.

During routine clinical outpatient investigation 16 of the 29 patients (10 men) (55.2%) gave a history of

Table 1. The causes of bile acid malabsorption determined in 84 patients by $^{75}\text{SeHCAT}$ scan at seven days between 1986 and 1994.

Cause	No. of patients	%
Idiopathic	29	34.5
Crohn's disease	22	26.1
Radiation enteritis	13	15.4
Ileal surgery	7	8.3
Post-cholecystectomy	7	8.3
Gastrectomy/Vagotomy	5	5.6
Ulcerative colitis	1	1.2
Whipple's disease	1	1.2
Food allergy	1	1.2
Total	84*	

* Two patients had both gastrectomy and cholecystectomy

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diarrhoea, defined as a distinct change in bowel habit with 4–15 loose watery motions per day dating from an episode of acute gastroenteritis. All recalled clearly and convincingly an episode of sudden onset gastroenteritis, usually severe enough to require hospitalisation or several days' confinement to bed. In six cases an enteric pathogen had been cultured in stools (campylobacter (4), salmonella (1), shigella (1)) (Table 2). In eight, the infection was contracted outside the UK. Other coexisting conditions included quiescent sarcoidosis (1), cholecystectomy five years after the onset of diarrhoea (1), ankylosing spondylitis on NSAID with no relationship to diarrhoea (1).

All patients were extensively investigated, but only the 16 with a history of gastroenteritis will be described in detail here. Prior to their ⁷⁵SeHCAT scan these patients were investigated on clinical grounds and not according to a protocol. Hence, faecal fat estimation was performed only in the 11 patients in whom steatorrhoea was suspected. Faecal fat excretion was raised in four of them, but their other pancreatic function tests were normal.

The mean age was 45.6 years (range 22–71). None of the patients had evidence of persistent enteric infection. Coeliac disease and giardiasis were excluded by distal duodenal biopsies and touch-smear cytology at endoscopy. Small bowel enema excluded Crohn's disease and other structural pathologies. All had

normal biopsies on fibresigmoidoscopy, and five had colonoscopy. No terminal ileal biopsies were obtained. Vitamin B₁₂ levels were estimated in all 16 cases, but were low in only two patients, both of whom underwent B₁₂ absorption tests. One was normal, the other had diminished B₁₂ absorption, with or without intrinsic factor, and without either intrinsic factor or gastric parietal cell antibodies. In this case, a lactulose breath hydrogen test was normal.

Among the 16 patients with less than 15% ⁷⁵SeHCAT retention, seven had 0–5% retention and one, 10–15% retention. All but one patient with a ⁷⁵SeHCAT retention of 10.3% responded to cholestyramine therapy (Table 2) in a dose range of 2–16 g/day, and all but one responded within the first week of treatment. The effect was sustained, but all but one patient had to continue with therapy.

Mean stool frequency was reduced from 7.2 per day to 2.1 per day ($p < 0.001$, paired *t*-test). Patients kept a record of stool frequency, mean stool frequency being assessed over a one-week period prior to treatment and two weeks after the start of treatment.

Discussion

In this study 29 (34.5%) of 90 patients with a positive ⁷⁵SeHCAT scan had no immediately obvious cause for their bile acid malabsorption. There was a clear

Table 2. Duration, origin and organism involved in the 16 patients with bile acid malabsorption.

Patient no.	Duration (years)	Origin of gastroenteritis	Organism	⁷⁵ SeHCAT % (abnormal <15%)	Ratio: stools to cholestyramine stools/day
1	8	UK	Campylobacter	7.9	15→3
2	0.5	Turkey	Nil	6.1	4→1
3	1	UK	Salmonella	9	5→1
4	5	UK	Campylobacter	10.3	6→6
5	18	UK	Nil	0	5→1
6	4	UK	Campylobacter	10.0	6→2
7	4	Egypt	Nil	2.0	5→1
8	6	France	Nil	2.6	8→3
9	1.5	Turkey	Nil	7.5	7→2
10	1.5	Gambia	Campylobacter	3.9	10→2
11	8	Israel	Shigella sonnei	2.1	12→3
12	1	UK	Nil	4	5→2
13	8	UK	Nil	0.2	5→2
14	0.25	Majorca	Nil	12	6→1
15	5	UK	Nil	2.3	8→2
16	8	Portugal	Nil	6.6	8→1
Mean	5.0	—	—	5.4	7.2→2.1*

* $p < 0.001$, paired *t*-test

Case 3: B₁₂ 158 ng/l (220–1,100), Dicopac test normal

Case 11: B₁₂ 169 ng/l (220–1,100), Dicopac test abnormal ± intrinsic factor

All others: within normal range

history of prolonged diarrhoea in 16 (55.2%) of the 29 patients dating from a confirmed or apparent episode of acute infective gastroenteritis. Such retrospective histories are open to the criticism of selective recall. It is not known how many patients with diarrhoea and a normal $^{75}\text{SeHCAT}$ scan might date the onset of their illness to a previous acute infective illness such as gastroenteritis. It cannot, therefore, be proved that gastroenteritis caused the subsequent bile acid malabsorption, but the emphatic and repeatable confirmation in our patients' histories, together with profound responses in all but one patient to bile acid sequestrants, suggest that the link is plausible and worthy of further investigation.

Although eight patients suffered their initial illness in such diverse places as Israel and Gambia, tropical sprue was excluded by normal distal duodenal biopsies, red cell folate levels and, in one case, a failure to respond to tetracycline. A diagnosis of postinfective irritable bowel syndrome might have been made if the patients had not undergone $^{75}\text{SeHCAT}$ testing.

Postinfective malabsorption is not a new concept. Malabsorption in general, and of bile acids in particular, can follow gastroenteritis in children [18]. Residual infections such as giardiasis must always be considered, but neither giardia nor any other enteric pathogen was detected. The $^{75}\text{SeHCAT}$ test is not influenced by concurrent small bowel bacterial overgrowth.

There are several possible explanations for our findings:

- increased bile acid production
- rapid small bowel transit overwhelming ileal reabsorptive capacity
- reduction in bile acid reabsorption.

The infective enteritides are well known to cause acute structural damage to the small intestine, particularly in the terminal ileum [19–21], which might lead to chronic impairment of ileal bile acid absorption because only the final 20 cm of terminal ileum actively reabsorbs bile acids. Increased hepatic synthesis compensates in part for the loss of bile acids, thereby further increasing exposure of the colonic mucosa to the secretory effects of bile acids.

It is important to note that even small reductions in terminal ileal bile acid absorption are amplified by the enterohepatic circulation and can lead to subnormal bile acid retention [1]. Therefore, the long-term damage to the terminal ileum need not be severe to cause bile acid malabsorption; this may explain why concomitant B_{12} deficiency was found in only two of the patients. Altered small bowel motility may allow insufficient time for active bile acid absorption, although preliminary studies with lactulose breath hydrogen tests do not indicate rapid transit. Finally, infective gastroenteritis might trigger an autoimmune response directed against terminal ileal bile acid receptors, analogous to the immune responses in re-

active arthropathies following infective gastroenteritis.

In this study, 16 of 29 patients with apparent idiopathic bile acid malabsorption gave a history of acute gastroenteritis of some severity. It seems unlikely that their acute gastroenteritis and bile acid malabsorption happened merely by coincidence. None of the patients had any bowel disturbance before the onset of acute enteritis, and they all dated their chronic diarrhoea to the episode of acute gastroenteritis.

The only consistently abnormal test in the 16 cases was the $^{75}\text{SeHCAT}$ scan. Their dramatic response to bile acid sequestrant therapy, often within the first 24 hours of treatment, indicates that the chronic diarrhoea was due to bile acid malabsorption.

The cut-off level of 15% for the seven-day $^{75}\text{SeHCAT}$ retention was set by Williams *et al* [17] in their extensive survey of bile acid malabsorption. They identified three groups of patients:

- all those with a seven-day retention of 0–5% responded to bile acid sequestrants
- there was a variable response in those with values of 5–10%
- no patient responded who had a value of 10–15%.

In our study, all the patients with values of 0–10% responded, as did one patient with a value of 12%. The one failure of treatment was associated with a retention of 10.3%. Our findings, therefore, accord well with those of Williams *et al*.

Our patients were investigated in routine outpatient clinics in a busy district general hospital; they were studied retrospectively and not according to a standard investigative protocol. We realise that infective diarrhoea, especially in patients travelling to certain parts of the world, is very common and also that our observations rely on patients' ability to recall the event. However, all the patients were absolutely certain that the onset of their symptoms followed an episode of gastroenteritis.

Our patients' response differs from that reported by Fordtran [23], whose patients with idiopathic chronic diarrhoea did not respond to cholestyramine, despite having impaired bile acid absorption as assessed by faecal ^{14}C -labelled taurocholic acid excretion. Others have stated that they have been unable to find any patients with chronic diarrhoea in whom bile acid malabsorption could be unequivocally blamed [24], but the study from the Edinburgh group [17] strongly supports our findings. Williams *et al* used $^{75}\text{SeHCAT}$ scans to identify, and cholestyramine to treat, idiopathic chronic diarrhoea with bile acid malabsorption. They concluded that their patients had an acquired defect of bile acid absorption, but did not identify causative factors. However, in two of their patients the history began whilst abroad so that an infective cause might be postulated.

We believe that we have identified a group of patients with the hitherto undescribed relationship between postinfective chronic diarrhoea or steatorrhoea and

bile acid malabsorption. This is presumed to be of terminal ileal origin, but we have no evidence of structural or other functional disturbance in that area. Ileal biopsies would have been of interest, and a prospective study is now being mounted, which will include terminal ileal biopsy. The cause of terminal ileal bile acid malabsorption remains to be determined, but due consideration should be given to this possibility in patients presenting with postinfective diarrhoea, many of whom may have suffered years of impaired quality of life as a result.

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