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Bile Acid Diarrhea: An Etiology of Chronic Diarrhea Easily Overlooked

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Chronic diarrhea is a symptom frequently noted in patients with various diseases. In addition to organic conditions, such as inflammatory bowel and neoplastic diseases, functional diseases including irritable bowel syndrome are important etiological factors related to chronic diarrhea. According to recent reports, approximately one-third of cases with suspected irritable bowel syndrome are actually diagnosed as bile acid diarrhea, which is characterized by decreased absorption of bile acids from the terminal ileum as well as their hepatic overproduction. Clinical signs and symptoms of bile acid diarrhea do not differ from those of other diseases complicated with chronic diarrhea, and reliable laboratory tests for proper diagnosis are not available in Japan. On the other hand, effective treatment is possible with oral administration of bile acid sequestrants. Therefore, in cases of irritable bowel syndrome with diarrhea and functional diarrhea, the possibility of bile acid diarrhea should always be considered, with a treatment trial with bile acid sequestrants discussed herein as an option.

Keywords: diarrhea, etiology, colestimide, bile acid, ileum

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INTRODUCTION

In normal healthy individuals without gastrointestinal symptoms, 70-80% of fecal volume is reported to be water. When the content of fecal water increases to greater than 80%, feces become softer and form muddy stools, with water content greater than 90% known to be associated with watery diarrhea. Although its definition is not uniform and patients cite various key symptoms, diarrhea is mainly defined as increased water content in stools, which is often accompanied by increased stool frequency [1]. Clinically, diarrhea is divided into acute and chronic. Acute diarrhea lasts less than four weeks and is mainly caused by an infectious, toxic, or food/drug-related pathological condition [1]. Since its etiology is not complicated, diagnosis and treatment are usually not difficult. On the other hand, etiological factors related to chronic diarrhea lasting over four weeks are diverse and pathogenetic diagnosis is often difficult [1, 2].

Endoscopy is widely employed for examinations of patients affected by chronic diarrhea. In those with bloody diarrhea and/or increased inflammatory markers, colonoscopy can detect etiological diseases with high sensitivity [3, 4, 5]. However, endoscopy findings are not adequately sensitive for such detection in non-bloody diarrhea cases, while the diagnostic yield of a colonoscopy examination for identification of etiological conditions is reported to range from only 15 to 31% [3, 4]. Addition of histopathological analysis of multiple biopsy samples obtained not only from colonic mucosa, but also from terminal ileal and duodenal mucosa will increase the diagnostic yield of an endoscopic examination, thus making diagnosis of microscopic colitis,

eosinophilic gastroenteritis, or celiac disease possible. Nevertheless, even with these precise clinical tools, identification of etiological factors related to chronic diarrhea is not easy and many patients remain undiagnosed [2].

When specific etiological conditions cannot be identified, chronic diarrhea cases are often diagnosed as functional diarrhea when abdominal pain is not present. On the other hand, for those with abdominal pain in addition to diarrhea, a clinical diagnosis of irritable bowel syndrome with diarrhea (IBS-D) is usually determined [2]. Recent studies have revealed that the cause in approximately 30% of cases with functional diarrhea or IBS-D is an increased colon concentration of luminal bile acids [6, 7].

Increased bile acid concentration in the colon is known to stimulate water and mucous secretion from colonic epithelial cells, and also augment colonic peristaltic activity, resulting in diarrhea [8, 9]. That caused by an increased colonic concentration of bile acids is termed bile acid diarrhea, which can be divided into two groups based on pathophysiology. In one, bile acid reabsorption is suppressed by the organic pathological condition of the terminal ileum, which massively absorbs bile acids, such as seen in cases of Crohn's disease and radiation enteritis, as well as in patients who have undergone a terminal ileal resection. In the other group, a functional abnormality of ileal absorption and/or hepatic overproduction of bile acids is considered to be responsible for the elevated colonic bile acid concentration [10, 11, 12]. In this review, the pathogenesis, diagnosis, and treatment of bile acid diarrhea is discussed.

PATHOGENESIS

Primary bile acids including cholic and chenodeoxycholic acid are synthesized from cholesterol in hepatocytes, and conjugated with glycine or taurine, then conjugated water-soluble primary bile acids are secreted though the biliary system in the duodenum. Bile acids have a variety of functions, including micellization of fat for easier access to lipase and bacteriostatic effects in the small intestine. In the terminal ileum, over 95% of conjugated primary bile acids are reabsorbed and return to hepatocytes though the portal venous system. This process of reusage of bile acids is termed enterohepatic circulation [13]. Only a small amount of bile aids enters the colon, where they are deconjugated and dehydroxylated at position 7α by colonic microbiota. As a result, secondary bile acids, deoxycholic acid and lithocholic acid, are synthesized from cholic acid and chenodeoxycholic acid, respectively. Deoxycholic acid stimulates colonic enterochromaffin cells via transmembrane G protein-coupled receptor 5 (TGR5) receptors and increases serotonin secretion, resulting in augmented colonic peristaltic movement [9, 14], while it also stimulates colonic luminal water secretion from colonic epithelial cells via TGR5-induced synthesis of cyclic AMP and cystic fibrosis transmembrane conductance regulator (CFTR) Cl channel opening [15]. In addition, deoxycholic and chenodeoxycholic acids are reported to decrease the sensory threshold to rectal distension and exaggerate defecation reflex in response to intra-rectal fecal contents [16]. Increased concentrations of colonic bile acids will cause diarrhea by increased water and mucous secretion, and augmented peristaltic activity (Fig. 1).

Bile acid absorption actively occurs in the terminal ileum and the majority of bile acids are absorbed in this gut segment [17]. Therefore, when terminal ileal function is damaged by a pathological condition, a large amount of unabsorbed bile acids enters the colon and causes bile acid diarrhea. Functional as well as organic pathological conditions can lead to bile acid diarrhea. Crohn's disease with terminal ileal lesions is a typical organic disease that causes decreased bile acid absorption in the terminal ileum, resulting in bile acid diarrhea. Indeed, a 5-15 times increased risk of development of bile acid diarrhea in patients with Crohn's disease has been reported [18]. Radiation enteritis caused by pelvic area radiotherapy has also been shown to be related to increased risk of bile acid diarrhea. As a functional pathological condition of the disease, conditions associated with post-infectious IBS-D are interesting. Inflammation is known to suppress gene expression of apical sodium-dependent bile acid and basolateral organic solute transporters [19, 20], which are critically important for active bile acid reabsorption in the terminal ileum and a decrease in these transporters is speculated to cause bile aid

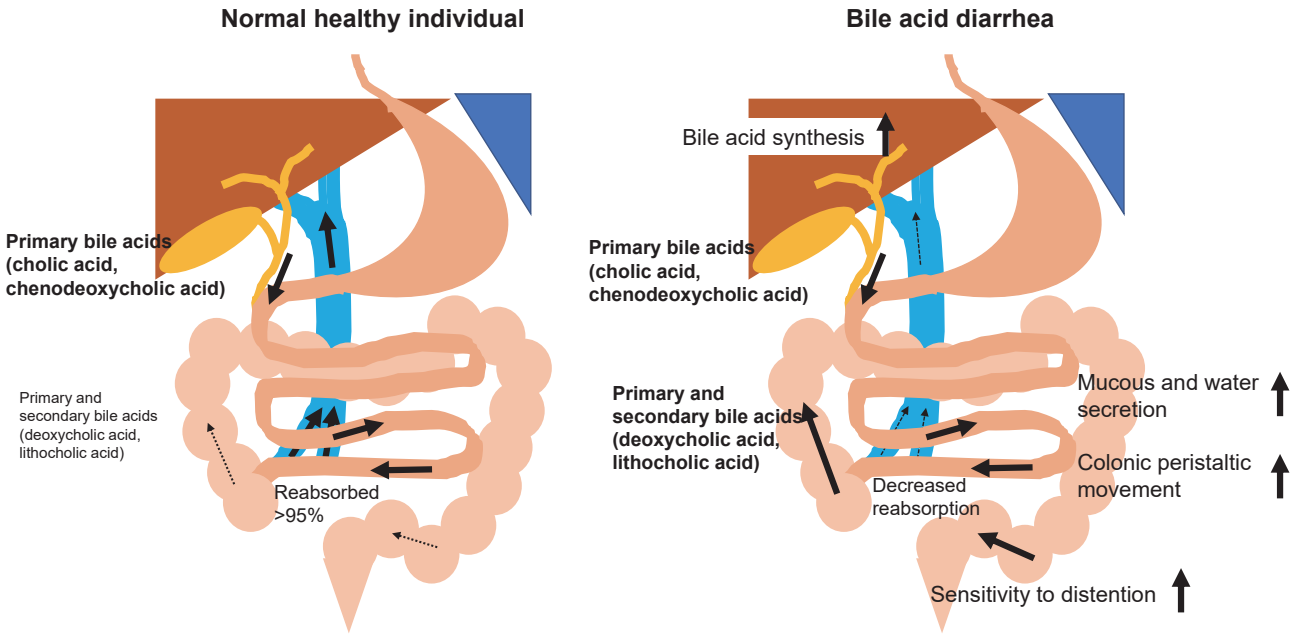

Fig. 1
Enterohepatic circulation of bile acids in normal individuals and patients with bile acid diarrhea. In cases of bile acid diarrhea, ileal reabsorption of bile acids is decreased, while their hepatic production is increased. A high concentration of bile acids in the colonic lumen causes diarrhea.

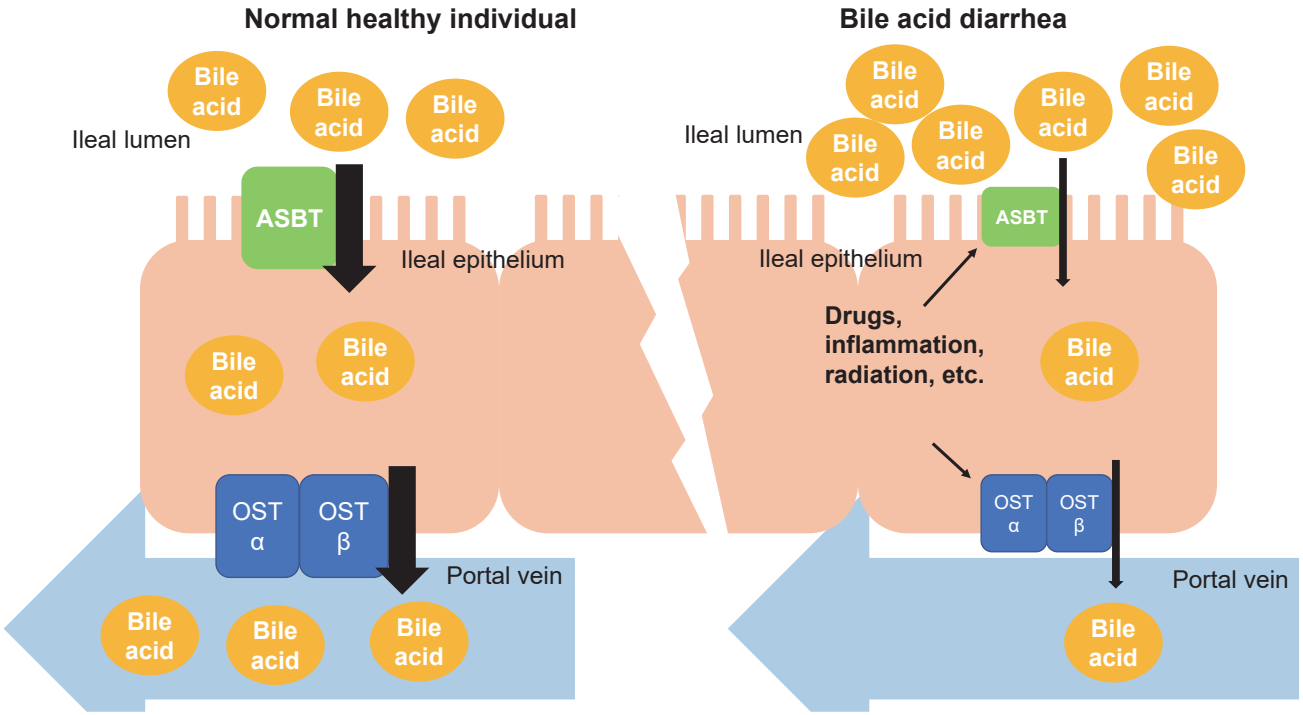

Fig. 2
Various factors are related to decreased gene expression of bile acid transporters and lower levels of bile acid reabsorption in cases with bile acid diarrhea.
ASBT: apical sodium-dependent bile acid transporter
OST: organic solute transporter

diarrhea (Fig. 2). Although the precise mechanisms related to occurrence are not completely understood, bile acid diarrhea has recently been reported to be a frequently observed etiology in chronic diarrhea cases [6,7].

DIAGNOSIS

Medical history taking

The presence of Crohn's disease, as well as history of ileal resection or radiation enteritis are important factors for increased risk for bile acid diarrhea. Furthermore, it is also important to ask regarding a past cholecystectomy [18, 21]. Additionally, administration of bile acids for treatment of such diseases as primary biliary cholangitis and that of elobixibat, an inhibitor of the apical sodium-dependent bile acid transporter used for treatment of chronic constipation, are shown to cause bile acid diarrhea [22].

Symptoms

Patients with bile acid diarrhea are known to have similar symptoms as those with other types of diarrhea. However, some investigators have suggested that symptoms reported by cases with bile acid diarrhea, such as abdominal pain, bloating, and fecal urgency, are prone to be less severe [23, 24], while stool consistency and gross appearance are also not characteristic features.

Physical examination

The diagnostic yield of a physical examination for bile acid diarrhea is limited. An examination of the abdomen may show the presence of surgical scars from an ileal resection or cholecystectomy, and skin lesions and/or arthritis are sometimes found in cases complicated with Crohn's disease.

Routine laboratory tests of peripheral blood and stool samples

A complete blood cell count and blood chemical analysis are routinely done for differential diagnosis of chronic diarrhea. However, in cases with bile acid diarrhea, no specific abnormality can be detected in these tests. Damage to the terminal ileum may be associated with decreased vitamin B12 concentration and increased bile acid synthesis possibly with decreased blood cholesterol level.

Determination of fecal electrolytes concentration is necessary for calculation of fecal osmotic gap, which suggests that bile acid diarrhea is categorized as a secretory diarrhea. Since several different types of diarrhea, including microscopic colitis, diabetic diarrhea, VIPoma, functional diarrhea, and IBS-D, are categorized as secretory diarrhea, a diagnosis of bile acid diarrhea based on fecal electrolyte values is difficult.

Specific tests for diagnosis of bile acid diarrhea

Several diagnostic methods have been developed specifically for diagnosis of bile acid diarrhea. Unfortunately, many are not available in Japan or not adequately sensitive for routine clinical use.

^{75}Selenium homocholic acid taurine (^{75}SeHCAT) test

A standard diagnostic test for bile acid diarrhea is efficacy assessment of bile acid enterohepatic circulation. In normal individuals, over 95% of secretory bile acids in the gut will be reabsorbed, mainly in the terminal ileum, then returned to hepatocytes for reuse as bile acids and finally secreted again in the gut. Mainly because of limited reabsorption of bile acids in cases with bile acid diarrhea, the efficacy of enterohepatic circulation is not adequate and orally administered radio-labelled bile acids will disappear from enterohepatic circulation within a short period. As a radio-labelled bile acid, taurine conjugated ^{75}SeHCAT acid is used for this test [25] and can be measured with a whole body counter. Following oral administration, it will remain in the body for a long period, with greater than 15% retention at seven days after administration in normal healthy individuals [26]. When retention is less than 5-10%, a diagnosis of bile acid diarrhea can be made. The sensitivity and specificity of this test are 87% and 93%, respectively, and it is used as a standard method for diagnosis of bile acid diarrhea in some European countries, where the test has been approved [21, 23, 27, 28]. However, several countries including Japan have yet to approve ^{75}SeHCAT testing for clinical use.

Plasma 7α-hydroxy-4-cholesten-3-one (C4) mea-

surement

C4 is an intermediate metabolite in the process of bile acids synthesis from cholesterol in hepatocytes and its plasma concentration increases with increased synthesis [29, 30]. In patients with bile acid diarrhea, hepatic synthesis of bile acids is known to be augmented to compensate for increased fecal loss of bile acids, thus the C4 concentration is expected to increase. According to previous studies, the sensitivity and specificity of C4 measurement for diagnosis of bile acid diarrhea are 40-85% and 71-85%, respectively, both of which are lower than those for the ^{75}SeHCAT test [29, 30]. In Japan, C4 measurement has not been approved for bile acid diarrhea diagnosis.

Plasma fibroblast growth factor 19 (FGF19) measurement

FGF19 is produced in the terminal ileum along with reabsorption of bile acids, then synthesized FGF19 reaches hepatocytes via the portal venous system and suppresses bile acid synthesis [29, 30]. This regulation is useful to control the size of the body pool of bile acids. In cases of bile acid diarrhea, because of decreased reabsorption of bile acids in the terminal ileum, the production and secretion of FGF19 will decrease, thus weakening its inhibition of hepatic bile acid synthesis. However, the technique used for measurement of FGF19 for diagnosis of bile acid diarrhea has a sensitivity of only 20% and specificity of 75% [29, 30]. FGF19 measurement has not been approved for diagnosis of bile acid diarrhea in Japan.

Measurement of excreted fecal bile acids

In bile acid diarrhea cases, fecal bile acid excretion will increase in response to decreased reabsorption in the terminal ileum. Therefore, increased excretion can be used for diagnosis of bile acid diarrhea. However, because of individual variations of fecal bile acid excretion, sensitivity and specificity are marginal at 66% and 80%, respectively [31].

Although several of these methods are available for diagnosis of bile acid diarrhea in western countries, none has yet received approval in Japan for routine clinical use. In addition, many are difficult to perform even in research laboratory settings. Therefore, in countries where ^{75}SeHCAT is not available, clinical guidelines often suggest empirical drug administration therapy when bile acid diarrhea cannot be ruled out from clinical findings [21].

TREATMENT

Various bile acid sequestrants are widely available, including Japan, and their administration is the standard treatment option for bile acid diarrhea in many countries [21, 32, 33]. On the other hand, use for bile aid diarrhea has not been approved by the Japanese regulating committee and precise informed consent must be obtained before beginning administration.

Dietary therapy

A low-fat diet has been investigated for decreasing bile acid secretion in the gut, though it has been found not to be effective enough for treatment of bile acid diarrhea. Thus, dietary therapy is presently not widely used.

Bile acid sequestrant therapy

Bile acid sequestrants are ion exchange resins that bind bile acids in the gut lumen after oral administration and prevent binding of bile acids to colonic epithelial TGR5 receptors [21, 32, 33]. After bounded with bile acid sequestrants, bile acids are excreted in the stool without being absorbed. These bile acid sequestrants are expected to help suppress colonic water secretion, decrease peristaltic movement, and improve diarrhea. Approval for use in Japan has been granted for decreasing plasma cholesterol level in routine clinical practice. As bile acid sequestrants, mainly two types of drugs are available in Japan, cholestyramine and colestimide.

Cholestyramine has long been used for hypercholesterolemia and given as a 44.4% powder, with 12 g/day the standard dose for treatment of hypercholesterolemia. For treatment of bile acid diarrhea, 2-24 g/day has been reported to be administered [21]. Although cholestyramine is effective and controls diarrhea within several days after starting administration, adherence to treatment is difficult, possibly because the drug must first be suspended in water for oral administration.

Colestimide is also given for hypercholesterolemia and provided as a 500-mg tablet, with the standard dose for treatment of bile acid diarrhea considered to be 3 g/day. This drug is effective for symptomatic control of bile acid diarrhea and administration adherence may be better as compared with cholestyramine. Both cholestyramine and colestimide can be used empirically for suspected cases of bile acid diarrhea according to clinical therapeutic guidelines in areas where ^{75}SeHCAT is not available [21]. Therefore, empirical administration of cholestyramine or colestimide is considered to be an acceptable option in Japan for diagnostic treatment of bile acid diarrhea. When cholestyramine or colestimide is administered to affected cases, diarrhea can be controlled in approximately 95%, though for long-term control, chronic continuous administration of bile acid sequestrants is necessary. It has been reported that only 6% of treated patients can stop taking bile acid sequestrants during the chronic course of the disease [21, 34]. Unfortunately, neither cholestyramine nor colestimide is approved for long-term treatment of bile acid diarrhea in Japan.

CHARACTERISTICS OF PATIENTS RECENTLY ENCOUNTERED

Table 1 presents nine cases of bile acid diarrhea treated in the two-year period from 2019 to 2020 at Steel Memorial Hirohata Hospital, Himeji, Japan. All of these patients were referred by other departments of our hospital, or came from other hospitals or clinics for investigation of chronic intractable diarrhea. Their ages ranged from 15 to 85 years, with a male/female ratio of 7/2, indicating a higher rate of incidence in males. Three were affected by atopic diathesis, while one patient had alcohol-related liver damage and another a history of surgical cholecystectomy. Various drugs were administered to control chronic diarrhea in these patients, though polycarbophil calcium, ramosetron, sulpiride, scopolamine, various probiotics, trimebutine, loperamide, etizolam, mepenzolate, various herbal medications, and digestive enzymes were found to be not effective.

The chief complaints of these patients with bile acid diarrhea were diarrhea and lower abdominal pain, whereas none reported bloody stools. Some noted that food intake was a trigger of diarrhea. The duration of diarrhea symptoms ranged from one to more than 60 months and over 50% of the patients reported symptoms lasting over one year. These findings indicate difficulties encountered with diagnosis of bile acid diarrhea. Laboratory test results of peripheral blood were not useful for diagnosis (Table 2). Inflammatory markers, albumin, total protein, and hemoglobin concentrations were all within normal ranges in these cases, and did not suggest the presence of inflammatory bowel or chronic infectious disease. Also, colonoscopy findings did not suggest a specific organic disease, while histopathological examinations of biopsy specimens obtained during colonoscopy did not suggest the presence of microscopic colitis, eosinophilic gastroenteritis, amyloidosis, or celiac disease.

A variety of clinical symptoms and signs can suggest functional bowel diseases, including functional diarrhea and IBS-D, thus differential diagnosis among functional diarrhea, irritable bowel syndrome, and bile acid diarrhea based on symptoms and signs is difficult. Unfortunately, specific laboratory tests for diagnosis of bile acid diarrhea, including ^{75}SeHCAT and plasma C4, FGF19, and fecal bile acid excretion measurements, are not available in Japan as part of routine clinical practice.

All nine patients presented in Table 1 were diagnosed with bile acid diarrhea, as each quickly responded to administration of the bile acid sequestrant colestimide. In cases clinically diagnosed as irritable bowel syndrome, several months are usually required for abdominal pain to be relieved, despite quick relief of diarrhea. Diarrhea in our patients was effectively controlled by colestimide administration, though when that was stopped, diarrhea returned and continuous administration was necessary for long-term control. During the two-year treatment period, no drug-related adverse event was observed in any of these cases. Adherence by each patient to the treatment protocol was good and none stopped taking colestimide regularly.

These results suggest that administration of bile acid sequestrants is effective and safe for bile acid diarrhea, in spite of difficulty with diagnosis.

Table 1. Clinical characteristics of nine patients with bile acid diarrhea

Age	Gender	Symptoms	Symptom duration (months)	History	Diagnosis when referred	Drugs not effective for diarrhea
22	M	Diarrhea, abdominal pain	>60	Hyperventilation syndrome, oral allergy syndrome	IBS-D	Calcium polycarbophil, ramosetron, sulpiride, Keishi-ka-shakuyaku-to
85	F	Diarrhea, abdominal pain	1	Ischemic colitis	IBS-D	Scopolamine, probiotics
66	F	Diarrhea	>60	Cholecystectomy	IBS-D	Keihi-ka-shakuyaku-to Trimebutine, probiotics, loperamide
17	M	Watery diarrhea, abdominal pain	6	Atopic dermatitis, allergic rhinitis	IBS-D	Calcium polycarbophil, Hange-shashin-to Hochu-ekki-to, Dai-kenchu-to
45	M	Diarrhea, abdominal pain	36	None related	IBS-D	Probiotics, etizolam, mepenzolate, scopolamine ramosetron,
65	M	Diarrhea	2	Alcohol-related liver damage	Functional diarrhea	Probiotics, digestive enzymes
39	M	Diarrhea, nausea	15	None related	IBS-D	Sulpiride, mosapride ramosetron, Rikkunshi-to
15	M	Diarrhea, abdominal pain	6	Polydactyly	suspected eosinophilic gastroenteritis	Prednisolone
26	M	Diarrhea	>60	Bronchial asthma	IBS-D	Ramosetron

IBS-D: irritable bowel syndrome with diarrhea

Table 2. Diagnosis and treatment of nine patients with bile acid diarrhea

Age	Gender	CRP	Hb (g/dl)	TP/Alb (g/dl)	Colonoscopy with histological study	Effective drug
22	M	Normal	15.0	7.6/5.2	Normal	Colestimide 3.0 g/day
85	F	Normal	12.8	6.6/3.8	Normal	Colestimide 1.5 g/day
66	F	Normal	15.0	7.2/4.2	Normal	Colestimide 3.0 g/day
17	M	Normal	16.7	7.0/5.0	Normal	Colestimide 3.0 g/day
45	M	Normal	14.9	7.4/4.6	Normal	Colestimide 3.0 g/day
65	M	Normal	13.0	6.7/4.0	Normal	Colestimide 3.0 g/day
39	M	Normal	16.4	7.4/4.3	Normal	Colestimide 1.5 g/day
15	M	Normal	13.8	6.7/4.2	Normal	Colestimide 3.0 g/day
26	M	Normal	-	-	Not done	Colestimide 3.0 g/day

SUMMARY

Bile acid diarrhea is caused by decreased bile acid reabsorption in the terminal ileum and hepatic overproduction of bile acids, and frequently found in cases clinically diagnosed as irritable bowel syndrome in Japan. Since differential diagnosis from irritable bowel syndrome based on clinical symptoms, signs, and routine laboratory test results is difficult, specific diagnostic tests are needed. In Japan, empirical administration of bile acid sequestrants is

presently the only specific diagnostic method available. Once diagnosis is established, continuous oral administration of colestimide, a bile acid sequestrant, has been found to be an effective and acceptable treatment for long-term control of the disease.

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