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Small Intestinal Manifestations of Diabetes Mellitus

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Diabetic diarrhea and steatorrhea occur predominantly in young adult males who have juvenile-onset diabetes mellitus complicated by neuropathy. The presentation is often severe, with nocturnal or postprandial watery diarrhea and tenesmus. Massive malabsorption of fat may occur; however, malabsorption of other nutrients and generalized wasting are quite rare. Because the symptoms are relatively refractory to treatment, it is important to rule out other, more easily treatable causes of this presentation. Bacterial overgrowth, exocrine pancreatic insufficiency, and celiac disease are also associated with diabetes mellitus and can mimic this process. Although the mechanism of diabetic diarrhea and steatorrhea remains unclear, neuropathy, gastrointestinal motor abnormalities, bacterial overgrowth, and bile acid abnormalities have been implicated in the pathogenesis.

Diabetic diarrhea and steatorrhea, although rare manifestations of diabetes mellitus, attain clinical importance because of their severity and refractory nature. Despite extensive investigation, the pathogenesis of this disorder remains unclear.

In 1926, in their discussion of gastric secretion in the diabetic, Bowen and Aaron [1] described ten patients with severe diarrhea. It was not until 1936, however, that this problem was recognized as constituting a distinct clinical entity. At that time, Bargen, Bollman, and Kepler [2] reported two cases of diabetic diarrhea that were refractory to therapy with pancreatic extract, and that were, therefore, presumed to be unrelated to pancreatic exocrine dysfunction. Since that time, direct measurement has confirmed that pancreatic enzyme secretion is normal in patients with diabetic diarrhea [3].

The association of this entity with the neuropathy of diabetes was recognized early. In 1945, while reviewing the clinical manifestations of 125 diabetics with neuropathy, Rundles [4] noticed the frequent occurrence of diarrhea, constipation, alternating diarrhea and constipation, or crampy abdominal pain. Twenty-two percent of the patients in that series had diarrhea.

The next year, Sheridan and Bailey [5] again recognized the clinical correlation of gastrointestinal symptoms with neuropathy in the diabetic. They described 40 patients with a history of poor diabetic control and neuropathy who developed intermittent nocturnal diarrhea with watery brown stools. Seventy-five percent of these patients had nocturnal incontinence.

Steatorrhea was first recognized as another presentation of this entity by Berge et al. [6] in 1956. The association with the neuropathy of diabetes persisted in this series. These patients presented identically to those with diabetic diarrhea who had normal fecal fat excretion. Bulky, malodorous stools were not seen, despite fecal fat

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levels as high as 70 g per day. Of note were the observations that these patients did not lose weight or appear wasted, and the biochemical parameters that are typically abnormal with malabsorption of other nutrients remained normal. The refractory nature of this lesion was again recognized after unsuccessful therapeutic trials of pancreatic enzymes, liver extract, anticholinergic agents, and corticosteroids.

This syndrome occurs in approximately one of every thousand diabetic patients (reports range from 0.001 percent to seven percent). There is a marked male predominance, despite the more frequent occurrence of diabetes in females than in males. The typical age of onset is between 36 and 42 years, among people with a history of prior diabetes for an average of eight years but with a range of a few months to several decades. Most patients have juvenile-onset diabetes and require insulin therapy.

The diarrhea is often severe, with up to fifty stools per day (typically ten to thirty), occurring particularly at night or when the patient is lying down. There also may be postprandial exacerbations. The character of the stool tends to be loose and watery, brown in color, and often associated with tenesmus. Most patients have unpredictable, intermittent symptoms. After a variable period of time, symptoms tend to become less severe in those patients with continuous manifestations, and exacerbations tend to become less severe and less frequent in patients with intermittent manifestations. Again, weight loss and wasting are unusual in these patients.

The best clinical correlates with diabetic diarrhea and steatorrhea are the following manifestations of diabetic neuropathy: orthostatic hypotension, impotence, retrograde ejaculation, bladder incontinence, anhidrosis, night sweats, muscle cramps, paresthesias, and loss of reflexes and vibratory sensation. Although other complications of diabetes such as nephropathy and retinopathy may also be present, these do not have a strong relationship with diarrhea.

DIFFERENTIAL DIAGNOSIS

In approaching the differential diagnosis of diarrhea in a diabetic patient, all of the unrelated causes of diarrhea must be considered. A careful history is particularly important to consider the osmotic diarrhea associated with ingestion of nonabsorbable hexitols. Diabetics can ingest large quantities of these in the form of snacks. Differentiation between diarrhea and steatorrhea should also be made. This may be done by performing a quantitative fecal fat determination on a timed sample while the patient ingests a standard diet of 100 g fat. The presence of steatorrhea, although completely compatible with this syndrome, might also be due to a more readily treatable cause, such as pancreatic insufficiency. For this reason, the presence of steatorrhea should lead to more extensive evaluation, possibly including gastrointestinal X-rays, biochemical tests of absorption, and small bowel biopsy.

Abnormalities of pancreatic exocrine function, including decreased secretory volume or enzyme output in response to stimulation by secretin or cholecystokinin, have been reported in twenty to forty percent of diabetic patients [7]. However, before pancreatic insufficiency can be held responsible for steatorrhea, enzyme output needs to be reduced to less than ten percent of normal [8]. This degree of pancreatic dysfunction has not been described in diabetes uncomplicated by pancreatitis. Conversely, diabetes mellitus is a common manifestation of chronic pancreatitis with pancreatic insufficiency. A clinical history of excessive alcohol intake or recurrent bouts of abdominal pain, or the presence of pancreatic calcification on plain abdominal radiograph, warrants direct evaluation of pancreatic exocrine function.

Although the association of diabetes with celiac disease has been cited widely, the reports have often been single case studies [9]. As the actual frequency of such cases is low, the significance of the association remains unclear. There might be a common genetic predisposition for both, as the incidence of the histocompatibility antigen HLA-B8 is higher than control levels (29 percent) in both celiac disease, where it is 80 percent [10] and juvenile-onset diabetes, where it is 54 percent [11]. Although the clinical presentations of celiac disease and diabetic diarrhea may be quite similar, there are differences which may serve as clues. The physician may suspect diarrhea is not of diabetic origin if there is: (*a*) the history of gastrointestinal symptoms preceding the diagnosis of diabetes, (*b*) the history of repeated episodes of hypoglycemia, (*c*) the absence of neuropathy, (*d*) the presence of anemia, (*e*) low serum folate concentration, (*f*) hypoalbuminemia, or (*g*) a malabsorption pattern on small bowel radiograph. Small bowel biopsy should be performed. If villous atrophy is present, a therapeutic trial of gluten-free diet is needed to document the diagnosis of celiac disease. Gluten-free dietary therapy has never been helpful for true diabetic diarrhea.

PATHOGENESIS

The pathogenesis of diabetic diarrhea remains obscure. Small intestinal morphology has been found to be normal at the light microscopic and electron microscopic levels [12,13]. The intestinal blood vessels show no evidence of microangiopathy [13], and there are no morphologic changes typically associated with intestinal ischemia.

The frequent clinical association with neuropathic findings may suggest a role for damage to the autonomic nervous system in the pathogenesis. Diarrhea certainly can occur with other processes affecting autonomic nervous function, such as vagotomy, sympathectomy, pheochromocytoma, and the administration of ganglionic blocking agents. Uncontrollable diarrhea and steatorrhea were reported to be present in a patient with amyloidosis involving the autonomic ganglia and myenteric plexus, but not involving the intestinal mucosa [14].

The neuropathologic findings in diabetic diarrhea have been studied by Hensley and Soergel [15]. They found two types of neural morphologic lesions associated with diabetic diarrhea—a hydropic neural change producing "giant sympathetic neurons" and the "dendritic swelling" of postganglionic neurons. The "giant sympathetic neurons" were felt to represent a nonspecific form of degeneration that is found also in alcoholic patients and in diabetic patients without diarrhea. The "dendritic swelling" was a more consistent sign of visceral neuropathy, but also was found in alcoholic patients and diabetic patients without diarrhea. Therefore, there appears to be no characteristic, pathognomonic, morphologic, neural abnormality in diabetic diarrhea. This certainly does not rule out a biochemical or functional abnormality.

Such an abnormality has been suggested to be present at the level of the interneural pathways in prevertebral and paravertebral sympathetic ganglia [3]. This group [3] found normal intestinal motility responses to epinephrine, norepinephrine, and methacholine in diabetics with diarrhea, which suggested normal efferent sympathetic and parasympathetic pathways.

Neural abnormalities might produce diarrhea via a direct effect on motor function. Indeed, abnormal intestinal motility in diabetics has been suggested by radiographic observations of gastric atony, segmentation and flocculation of the barium column, and increased transit time [16]. Small bowel motility in diabetics

with and without peripheral neuropathy and in those with and without diarrhea was studied by McNally, Reinhard, and Schwartz [16]. They found onset of symptoms of the peripheral neuropathy to be correlated with progressive decrease in upper small bowel tone, as well as increase in frequency and amplitude of large peristaltic waves. There were not sufficient patients with diabetic diarrhea in their group to assess the role of motor disorders in the pathogenesis of this lesion.

Although slowed intestinal transit cannot be linked directly to the production of diarrhea, it can be linked indirectly, mediated by resultant bacterial overgrowth. Other disorders such as scleroderma, postgastrectomy steatorrhea, jejunal diverticulosis, and blind loop syndrome which have abnormal bowel motility can have associated bacterial overgrowth and malabsorption. The role of intestinal bacteria in the pathogenesis of diabetic diarrhea was suggested by Malins and French [17], who observed dramatic improvement in several patients treated with a broad spectrum antibiotic. However, the unpredictable course of diabetic diarrhea makes this observation difficult to interpret. Green, Berge, and Sprague [18] performed a double-blind study to evaluate the efficacy of antibiotic therapy for diabetic diarrhea and found that some patients had symptoms which improved with antibiotics and which recurred on placebo. Although not all patients responded, enough did to warrant a therapeutic trial. These observations were confirmed by Goldstein, Wirts, and Kowlessar [19] who also cultured upper gastrointestinal aspirates. Their work also confirmed the lack of bacterial overgrowth in the majority of patients with diabetic diarrhea. The ^{14}C-glycocholate breath test can be used to predict which diabetics have bacterial overgrowth and would benefit from antibiotic therapy [20].

Bile acid abnormalities have also been thought to play a role in the pathogenesis of diabetic diarrhea [21]. Molloy and Tomkin [21] have found that diabetics with neuropathy have an enlarged bile salt pool with increased dihydroxy bile salts and increased fecal bile salt excretion compared to normal controls. The diabetics with diarrhea developed a smaller bile salt pool. This was interpreted to suggest an intermittent cholereic enteropathy. However, other authors have not confirmed the increase in fecal bile salt excretion in diabetics with diarrhea [20], and cholestyramine, a bile salt-binding resin, has not helped the majority of patients.

TREATMENT

Treatment of diabetic diarrhea is often not effective. Therapeutic trials have been difficult to interpret due to the intermittent and unpredictable clinical course of this disorder. An important phase of treatment is making sure a treatable cause of diarrhea is not being missed.

Careful diabetic control is recommended, based on the observations that some forms of diabetic neuropathy are reversible and that some recurrences of gastrointestinal symptoms have been associated with prolonged periods of poor diabetic control. There is no evidence, however, that good control of the diabetes will improve the diarrhea. There is a recent report that hypoglycemia may contribute to the gastrointestinal manifestations, and that a reduction of insulin dose has a beneficial effect on some patients [22].

As mentioned above, a therapeutic trial of antibiotics is worthwhile, although many patients do not improve on this regimen. The type of antibiotic and dosage regimen have not been critically evaluated. Tetracycline has been effective with an initial dose of 1 g daily, tapered to 250 mg daily as a maintenance or intermittent dose.

Most therapy is symptomatic, using antidiarrheal agents such as diphenoxylate hydrochloride or psyllium hydrophilic mucilloid powder.

CONCLUSIONS

Diabetic diarrhea and steatorrhea can be a severe complication of diabetes mellitus, one which can be extremely debilitating and refractory to therapy. The mechanism of this remains unclear, although neuropathy, gastrointestinal motor abnormalities, bacterial overgrowth, and bile acid abnormalities have been implicated in the pathogenesis. It is particularly important to rule out other, more easily treated causes of this presentation in diabetic patients, before attempting symptomatic therapy.

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