Diabetes and the Gastrointestinal Tract in the Pediatric Patient

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INTRODUCTION

The child who has diabetes is at increased risk for gastrointestinal disorders. In addition to the typical stigmata of increased weight and round, robust-appearing faces with chemical abnormalities of hypoglycemia, hypocalemia, and hyperbilirubinemia, the infant of a diabetic mother may have a microcolon which requires immediate diagnosis and treatment. Although these disorders complicate the neonatal period, they resolve rapidly and later in life, the liver, intestine, and pancreas may each be affected in the child who develops juvenile diabetes. Celiac disease and cystic fibrosis are common disorders in the pediatric patient and have an increased association with diabetes. A currently popular dietary measure in children with diabetes, the use of “sugarless candy,” may result in diarrhea. This article will familiarize the clinician with these associations and allow a more knowledgeable approach to the gastrointestinal problems of the child with diabetes.

PATHOGENESIS OF JUVENILE DIABETES

The pathogenesis of juvenile-onset diabetes is thought to be different from that of maturity-onset diabetes. Juvenile-onset diabetes occurs in a younger age group, the onset is more abrupt, patients require insulin administration early in the course of the disease, and a seasonal incidence has been suggested. In a large number of patients with juvenile diabetes, especially early on in the course of the disease, inflammatory cells are seen to collect around the islets of Langerhans [1]. All of these factors have prompted speculation about the temporal relationship to a viral infection. A number of reports have identified a relationship between the onset of a viral infection such as mumps and the subsequent development of diabetes [2]. There are case reports noting culture of rubella virus from the pancreas of a patient who has contracted diabetes [3]. Recently, a coxsackie B4 virus was identified in the pancreas of a 10-year-old child who developed diabetic ketoacidosis [4] and there have been reports of increased titers to coxsackie viral infections in patients with
diabetes [5]. The issue clearly requires further study, but it remains possible that a number of patients with juvenile diabetes may be manifesting endocrine pancreatic insufficiency as the sequela to a viral pancreatitis.

There are also reasons to promote an autoimmune phenomena as the basis for juvenile diabetes mellitus [6]. Inflammatory cells around the islets are consistent with an autoimmune process and several autoimmune disorders (i.e., Hashimotis, thyroiditis, juvenile rheumatoid arthritis) are associated with insulin-dependent diabetics. Antibodies to pancreatic islet cells, as well as several other body organs, can be demonstrated in many newly diagnosed juvenile diabetics. Cell-mediated immunity to the pancreas can also be demonstrated in many patients [7,8].

There is a definite genetic predisposition to the development of juvenile diabetes. The strongest HLA associations for patients with juvenile diabetes are seen with DRW3 and/or DRW4 cell surface antigens. The presence of DRW3 increases the risk of developing juvenile-onset diabetes mellitus 3.8 times [9].

THE PANCREAS AND JUVENILE DIABETES

Acute Pancreatitis

Pancreatitis is not a common cause of abdominal pain in the pediatric age group. There is some evidence to suggest, however, that the incidence of pancreatitis is increased in the patient with juvenile diabetes, and it should be considered in the differential diagnosis of any patient presenting with ketoacidosis with abdominal pain that does not resolve appropriately in the course of medical management [10].

The child with diabetic ketoacidosis often presents with abdominal pain that is not associated with pancreatitis. This pain is generalized in location. The abdomen may be mildly tender to deep palpation but should not be rigid or exhibit rebound tenderness. The child in diabetic ketoacidosis may have a partial ileus resulting in nausea and vomiting, which may require placement of an NG tube. The gastrointestinal manifestations of diabetic ketoacidosis should subside within six hours after the institution of intravenous fluid administration, correction of electrolyte abnormalities, and insulin therapy.

The child who has acute pancreatitis in addition to his diabetic ketoacidosis may give a history of a more sudden onset of abdominal pain. The pain is usually much more severe in the upper abdomen and may be associated with extreme tenderness, rigidity, and often rebound tenderness. Nausea and vomiting are often present in the child with pancreatitis.

The diagnosis of acute pancreatitis can be confirmed by elevated serum amylase and lipase levels. Amylase levels rise most rapidly and lipase levels often do not increase for 24-48 hours. The urinary amylase-to-creatinine clearance ratio may not be as helpful in the diagnosis of acute pancreatitis in the patient with juvenile diabetes, as it may also be elevated in diabetic ketoacidosis. Patients with acute pancreatitis are also likely to have increased leukocyte count, fever, decreased serum calcium, and are likely to become volume-depleted very rapidly. In the patient where laboratory values are equivocal, a flat plate of the abdomen may reveal the sentinel loop typical of pancreatitis, or ultrasound may reveal inflammation within the body of the pancreas.

The tendency of the patient with acute pancreatitis to become volume-depleted in addition to the dehydration secondary to the ketoacidosis makes him at high risk. Treatment of pancreatitis and juvenile diabetes mellitus with or without ketoacidosis consists of prompt parenteral fluid administration and insulin therapy. Patients
should be made NPO, have nasogastric suction placed, and will often require analgesia for treatment of the pancreatitis. We do not recommend prophylactic antibiotics for the patient with pancreatitis. The patient should be kept NPO until resolution of the pancreatitis is indicated by return of serum amylase and lipase to near normal values. Patients with complicated or prolonged courses of pancreatitis must be followed carefully by ultrasound in order to detect the formation of a pseudocyst or abscess, which may require surgical intervention.

Pancreatic Insufficiency

With the exception of cystic fibrosis, pancreatic insufficiency is extremely uncommon in the pediatric age group. Although there have been isolated case reports of idiopathic, clinically detected pancreatic insufficiency in children with growth failure who have later developed diabetes, it is extremely uncommon to have clinical evidence of pancreatic insufficiency in a child with juvenile diabetes [11].

Even though it is rarely a clinical problem, studies to quantitate pancreatic function in terms of bicarbonate, trypsin, and amylase secretions have shown significant loss of exocrine pancreatic function in 80 percent of patients who have had juvenile diabetes for five years [12]. The longer the duration of juvenile diabetes, the more severe the exocrine pancreatic dysfunction. It is possible that the exocrine pancreatic dysfunction is a result of progressive structural damage to the diabetic pancreas. The pancreas in juvenile diabetes is sometimes atrophic, infiltrated with fat, and inflammatory infiltrates have become observed throughout the pancreas. Another contributing factor may be that insulin is necessary to regulate the synthesis of pancreatic amylase and the lack of insulin's trophic effect may result in a decrease of pancreatic enzymes.

THE LIVER AND JUVENILE DIABETES

Over 50 years ago Mauriac's syndrome was described, in which juvenile diabetics had dwarfism, hepatosplenomegaly, and obesity [13]. The hepatosplenomegaly was quite striking and often extended into the pelvis. The syndrome is seen exclusively in patients with extremely poor control of their diabetes. Current developments in insulin therapy which allow a more physiologic control of glucose homeostasis have made the occurrence of this syndrome extremely rare. It has been suggested that in Mauriac's syndrome the hepatomegaly is secondary to increased glycogen and/or lipid storage [14]. Recent data suggest that the poor growth and dwarfism seen in these patients may be related to low somatomedin levels which are improved by a more physiologic control of glucose levels [15].

Clinically, liver disease is rarely a problem in the juvenile diabetic; however, if careful attention is paid to the histology of the liver, a large number of abnormalities may be found. In addition to revealing amounts of fat and glycogen infiltration which seem to correlate with metabolic control, evidence of acute and chronic inflammation has been reported in a large percentage of patients [16].

JUVENILE DIABETES AND THE INTESTINAL TRACT

Most children with juvenile diabetes have normally appearing intestinal villous structure on examination by light microscopy. Diabetic gastroenteropathy, a syndrome of intermittent or persistent diarrhea with or without steatorrhea, is usually associated with a moderate to severe neuropathy and is seen in patients with long-standing diabetes [17]. This condition is rarely seen during childhood.
The examination of the small intestinal epithelium by special fat stains has revealed an increased amount of lipid in diabetic children when compared to normal controls [18]. It is not certain whether this is secondary to a defective clearing of exogenously absorbed lipid due to abnormal villous contracture, or due to markedly increased endogenous synthesis of lipid. It has been speculated that a defect of lipid clearance may be an early manifestation of autonomic neuropathy, which would be the precursor of the diabetic gastroenteropathy seen in long-standing diabetics [19]. There appears to be no relationship between the degree of accumulation of lipid in the intestinal mucosa and the duration of the diabetes or the subjective gastrointestinal symptomatology such as abdominal pain. The amount of lipid present in the small intestine appears to correlate most closely with the quality of control of the diabetes [18].

THE SMALL LEFT COLON SYNDROME

The small left colon syndrome (SLCS) was first described in 1974 and later pursued in detail by Stewart et al. [20]. It occurs in infants born to diabetic mothers, most of whom are insulin-dependent. There is often a prenatal history of maternal toxemia or polyhydramnios and the infants are born between 36 and 40 weeks of gestation. Birth weights have varied between 2,400 and 4,500 g. Not all babies are symptomatic, and up to 40 percent of infants born to diabetic mothers have radiologic evidence of this disease. Initially there is respiratory distress and evidence of hypoglycemic cardiomyopathy, persistent fetal circulation, and abdominal distension. They fail to pass meconium by 48 hours. The disease is a formidable one, for 50 to 75 percent of infants reported have had intestinal perforation, and the mortality may be as high as 50 percent. Radiologic study shows dilated loops of small bowel and right colon, suggesting distal colonic obstruction. Barium enema shows decreased caliber of the colon from the anus to the splenic flexure with a long transition zone. The colon proximal to the area of obstruction is dilated and fills easily with barium. Pathologic studies show an increase in the ratio of small cells to multipolar ganglion cells in both right and left colonic tissue. It has been suggested that the etiology lies in an abnormal glucagon response to neonatal hypoglycemia, for the high glucagon levels are not influenced by intravenous glucose [21]. It is proposed that the increased glucagon inhibits gastrointestinal motility, particularly in the jejunum and in the sigmoid. It is also possible that the immature ganglion cells are unable to respond to normal sympathetic stimulation.

A Gastrografin or Hypaque enema is both diagnostic and therapeutic, but several enemas may be required. Perforations occur in those symptomatic for 24 hours before treatment.

JUVENILE DIABETES MELLITUS AND CELIAC DISEASE

It appears that children who have juvenile diabetes mellitus are at increased risk to suffer celiac disease [22]. There seems to be a genetic predisposition to both celiac disease and juvenile diabetes, with both sharing an increased incidence of certain histocompatibility antigens such as HLA-B-8. Approximately 80 percent of patients with celiac disease are positive for HLA-B-8 while only 20–30 percent of the normal population is positive for this antigen [23]. During an eight-year period, 100 new cases of celiac disease and 400 new cases of juvenile diabetes were reported at the Hospital for Sick Children in Toronto. The occurrence of juvenile diabetes in 6 percent of children with celiac disease and celiac disease in 1.57 percent of the children
with diabetes was much higher than one would expect from the prevalence of these disorders in the general population [24].

Celiac disease occurs in approximately 1 in 3,000 in the United States; this figure varies throughout the world, reaching a high of 1:300 in western Ireland. The disease appears to affect primarily Caucasians, although various ethnic groups have been reported to have celiac disease [22].

The pathogenesis of celiac disease remains unclear, although it is known that gluten, a complex germ protein molecule found in wheat and several other cereals, has a toxic effect on small intestinal epithelium. This toxic effect on the small intestinal epithelium causes the malabsorption which is the hallmark of many of the clinical stigmata of celiac disease.

Celiac disease is usually diagnosed in the pediatric age group between eight months and two years presenting with steatorrhea and failure to thrive. It is worthy of note that one can present with steatorrhea and not have diarrhea. A second group of patients will present in the pediatric age group in early adolescence with short stature and delayed sexual development. Diagnosis of celiac disease is suggested by several laboratory parameters which indicate malabsorption. A decreased serum carotene suggests fat malabsorption; a decreased RBC folic acid level will indicate decreased small intestinal absorption of water-soluble vitamins; an abnormal xylose absorption test will indicate impaired small intestinal function, anemia may indicate iron deficiency, a prolonged prothrombin time may indicate hypoprothrombinemia secondary to vitamin K malabsorption, and a 72-hour stool fat collection will reveal less than 95 percent absorption of ingested fats. The diagnosis of celiac disease requires a small bowel biopsy which reveals increased mototic activity in the glandular epithelium, an inflammatory response in the lamina propria noted as a round cell infiltrate; immature epithelial cells which may appear pseudostratified, cuboidal, or even squamous; and a decreased villous-to-crypt ratio.

The elimination of gluten-containing products from the child's diet usually leads to a rapid clinical response. Initially, restriction of lactose is advised for several weeks until disaccharidase values return to normal and the child is less likely to have lactose intolerance. It is essential that the child and family visit a well-trained dietician or nutritionist initially and at yearly intervals. Even the most intelligent and well-meaning parents are unable to keep up with constant changes that occur in commercial foods.

**JUVENILE DIABETES AND CYSTIC FIBROSIS**

Cystic fibrosis is the most common cause of pancreatic insufficiency in the pediatric age group, accounting for greater than 95 percent of such cases. The primary etiology of cystic fibrosis is unknown but the clinical manifestations of pancreatic insufficiency and lung disease are secondary to thick tenacious mucous which has abnormal viscosity. It is a genetically determined, autosomal recessive disorder, which manifests itself approximately 1 in 2,000 Caucasian births. Most children with cystic fibrosis are diagnosed in early childhood subsequent to evaluations for failure to thrive, chronic diarrhea, or recurrent pneumonia. The diagnosis is made by an elevated sweat chloride concentration which can be performed in any major pediatric center.

At least 50 mg of sweat is needed for adequate analysis and a sweat chloride of 60 meq/l or higher is diagnostic of cystic fibrosis. Pancreatic insufficiency is present in about 90 percent of infants with cystic fibrosis [25]. If a sweat collection is impos-
sible to obtain, stool trypsin can be measured. Most infants' stools contain trypsin in dilution of 1:100 but as transit time increases in older children the enzyme is degraded by colonic bacteria and is no longer present.

In 1962, when the association between cystic fibrosis and diabetes mellitus was first noted, the incidence was approximately 1 to 130 patients. Since then the average life expectancy of a patient with cystic fibrosis has greatly increased and the two disorders are seen more commonly, especially in older patients with cystic fibrosis.

Recently as many as 75 percent of patients with cystic fibrosis had been reported to have abnormal glucose tolerance tests. A group of adolescent males with relatively mild cystic fibrosis were compared to healthy adolescent males and found to have significantly impaired glucose tolerance and significantly lower serum immunoreactive insulin levels during oral and intravenous glucose tolerance tests [26]. This same study demonstrated that patients with cystic fibrosis were even more sensitive than normals in the peripheral response to administered insulin, suggesting that the impaired carbohydrate tolerance seen in cystic fibrosis is due to an impaired insulin response to a carbohydrate load. The increased peripheral tissue sensitivity to insulin may help explain why patients with cystic fibrosis and diabetes rarely have problems with ketoacidosis.

This impaired insulin response in cystic fibrosis is not thought to be the same disorder as juvenile diabetes mellitus but rather secondary to disordered architecture and fibrous replacement of pancreatic islets. Although at autopsy a patient with cystic fibrosis may have renal lesions similar to those of juvenile diabetics, the diabetes usually has no effect on the longevity of children with cystic fibrosis. The child with cystic fibrosis and diabetes mellitus is not as difficult to control as the normal juvenile diabetic.

The management of intestinal manifestations of cystic fibrosis requires pancreatic enzyme replacement. Recently enteric-coated granules have become available and allow pancreatic enzyme to be ingested in a much more palatable and efficient manner. The pulmonary disease in cystic fibrosis requires management by a clinician who specializes in this disorder.

Shwachmann's syndrome is a much less common syndrome occurring in the pediatric age patient with manifestations of pancreatic insufficiency, normal sweat electrolytes, short stature, and neutropenia. Although not the rule, diabetes mellitus can occur in these patients [27].

**JUVENILE DIABETES AND OSMOTIC DIARRHEA**

In recent years the use of so-called sugarless candies and soft drinks has become common. Many patients with juvenile diabetes include these products in their dietary regimen for prophylaxis of dental caries. Sorbitol is the most commonly used, so-called "sugarless" sugar; it is a naturally occurring sugar which may be found in small quantities in fruits, vegetables, and berries. It is not metabolized by the oral flora and is very slowly absorbed through the gastrointestinal tract. Because of these very properties diarrhea may follow, after the ingestion of sufficient quantities of these sugars. It has been demonstrated that many children can develop diarrhea after the ingestion of approximately 9 grams of Sorbitol. The diarrheal threshold appears to be related to weight and this may be easily exceeded by the energetic appetites of children. One pack of Sorbitol-containing mints can easily cause diarrhea in a young child [28].
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