Enteropathies of infancy

Pierre Russo

Abstract

Enteropathies of infancy constitute a heterogeneous group of disorders which are difficult to diagnose and to manage. The intestinal biopsy is a cornerstone in the investigation of many of these patients, and the role of the pathologist can be pivotal in establishing the diagnosis. Many of the entities that cause severe enteropathy of infancy have been recognized only in the last several decades. Though rare, the study of these disorders has yielded important insights into enterocyte development and function, and intestinal immunity and tolerance.

Keywords chronic diarrhoea; enteropathy; intestinal biopsy; intractable diarrhoea; malabsorption

Introduction and general remarks

The aims of this article are to review the entities that cause severe chronic diarrhoea and failure to thrive in infancy and to illustrate their appearance on gastrointestinal biopsies. Many of the disorders described herein cause "*intractable diarrhoea of infancy*", a term coined by Avery and colleagues in 1968 to describe cases of severe chronic diarrhoea in neonates and infants, most of which remained undiagnosed and which were associated with a high mortality at that time.[1] Over the last few decades, the use of parenteral nutrition, immunosuppression and better control of infectious complications has allowed improved survival of these patients which, combined with the more widespread use of endoscopy and better investigational tools, has resulted in the description of a number of entities causing severe enteropathy. As therapeutic options have diversified to include intestinal transplantation, these diseases require prompt and accurate diagnosis and need to be distinguished from infections and food allergies, which are more amenable to conventional treatment. The disorders which are the focus of this chapter are outlined in Box 1. Celiac disease will not be considered in this review as it is not, strictly speaking, a disorder of infancy, is not significantly different histologically in children and adults and many excellent reviews on this entity are available.

The type of diarrhoea may point to the aetiology and orient the diagnostic work-up.[2,3] ***Osmotic*** diarrhoea results from the presence of unabsorbed or poorly absorbed solute in the gut. There is an osmotic "gap" in stool analysis ($2 \times [Na^+ + K^+] < 280$ mOsm) signifying unmeasured particles, usually sugars and low molecular weight compounds. Typically, the diarrhoea resolves with bowel rest or removal of the offending solute. Congenital carbohydrate transport and enzymatic disorders, such as disaccharidase deficiency, are causes of osmotic diarrhoea.

Pierre Russo MD *Professor, Department of Pathology and Laboratory Medicine, The University of Pennsylvania School of Medicine; Director, Division of Anatomic Pathology, The Children's Hospital of Philadelphia, Pennsylvania, USA. Conflicts of interest: none declared.*

Secretory diarrhoea, on the other hand, results from abnormal secretion of electrolytes into the lumen. It can be primary or secondary, with the latter due to severe mucosal injury causing impairment of water and electrolyte absorption. Secretory diarrhoea does not resolve with bowel rest. It can result from congenital defects of ion absorption such as Na^+/Cl^- diarrhoea, loss of intestinal surface area due to diffuse mucosal disease, and abnormal circulating mediators including enteric hormones, neuropeptides, and bacterial enterotoxins.

Biopsy sampling and indications in children

In current paediatric gastrointestinal practice, intestinal biopsies are most frequently obtained from the duodenum via forceps during endoscopic examination, during which biopsies are also obtained from the oesophagus and stomach (EGD). Endoscopic forceps biopsies have largely replaced the Crosby suction biopsies because of greater ease of the procedure, patient comfort, avoidance of radiation exposure, direct visualization of the GI tract and the possibility of obtaining multiple biopsies from several sites. In addition to obtaining biopsies for routine histology, samples may also be snap-frozen (for disaccharidase analysis) or submitted for electron microscopy (for confirmation of microvillous inclusion disease). The intestinal biopsy may reveal characteristic changes in some entities (fat-filled enterocytes in abetalipoproteinemia), may show variable degrees of villous atrophy with or without inflammation, or, as with congenital transport disorders, may be normal (Table 1). Biopsies from both proximal and distal duodenum are recommended, including biopsies of endoscopically normal mucosa, as many disorders affecting the duodenum may have a focal distribution.

As paediatric EGD has evolved into a routine outpatient procedure, the indications for its use have correspondingly changed. At The Children's Hospital of Philadelphia, the first-time EGD

Enteropathies of infancy

Congenital transport and enzymatic deficiencies

- Glucose-galactose malabsorption
- Disaccharidase deficiency
- Lysinuric protein intolerance
- Abetalipoproteinemia
- Chylomicron retention disease
- Sodium–chloride diarrhoea
- Primary bile acid malabsorption

Disorders of epithelial differentiation

- Microvillus inclusion disease
- Tufting enteropathy
- Enteroendocrine cell dysgenesis

Autoimmune enteropathy
Tricho-hepato-enteric syndrome
Eosinophilic gastroenteritis

Box 1

Diagnostic findings on small intestinal biopsies

Intestinal biopsy	Differential diagnosis
Normal	Sucrase–isomaltase deficiency
	Congenital lactase deficiency
	Fructose malabsorption
	Glucose galactose malabsorption
	Congenital Na^+/Cl^- diarrhoea
Inflammatory lesions ± villous atrophy	Celiac disease
	Autoimmune enteropathy
	Protracted infectious diarrhoea
	Immunodeficiency states (most)
	Bacterial overgrowth
	Cow's milk or soy protein intolerance
	Chronic inflammatory bowel diseases
Specific lesions	
• Fat filled enterocytes	A beta lipoproteinemia
	Anderson's disease
• Ectatic lymphatics	Lymphangiectasia
• Dense inspissated mucus	Cystic fibrosis
• Epithelial abnormalities	Microvillus inclusion disease
	Tufting enteropathy
• Eosinophils	Eosinophilic gastroenteritides
• Absence or paucity of inflammatory cells	Severe combined immunodeficiency
	Agammaglobulinemia

Table 1

rate increased 12-fold in a 20 year interval between 1985 and 2005, with isolated abdominal pain replacing GI bleeding as the most frequent indication.[4] The most frequent indications for EGD and colonoscopies in children less than 1 year of age, according to a recent study, were diarrhoea, failure to thrive, reflux and rectal bleeding.[5] Histological abnormalities were detected in two-thirds of cases, whereas only 2% of mucosal biopsies were insufficient. Sampling even endoscopically normal-appearing mucosa is recommended, as it may help assess the "background" features of the mucosa, and histological examination may reveal clinically relevant findings unsuspected by the endoscopist (e.g. granulomas).[6,7]

Congenital disorders of intestinal transport and absorption

Except for those disorders associated with fat trafficking, small intestinal biopsies in most congenital disorders of transport are generally normal or only very slightly abnormal. Therefore, a normal appearing small bowel mucosa from a patient with prolonged diarrhoea, especially a young infant, should alert the clinician to a consideration of these entities. A number of specific gene defects associated with various disorders of substrate transport have been recently characterized and have been instrumental in providing a picture of enterocyte function at the molecular level.[8]

The clinical picture of **congenital disaccharidase deficiency** and **glucose–galactose malabsorption** is an osmotic diarrhoea due to the unabsorbed solute in the ileum. The diagnosis is obtained by the determination of disaccharidase activities in homogenates of small bowel biopsies or by breath-testing. Congenital disaccharidase and transporter deficiencies are rare; much more common are secondary lesion that result from diffuse mucosal damage due to infectious gastroenteritis, gluten-sensitive enteropathy, or food allergies.

Except for **lysinuric protein intolerance (LPI)**, disorders of **amino acid transport** rarely feature prominent gastrointestinal manifestations. LPI results from mutations in the *SLCA7* gene that codes for the dibasic amino acid transporter system,[9] and it clinically manifests as failure to thrive with vomiting and diarrhoea. One 5 year old boy reportedly had chronic diarrhoea and a flat gut on small intestinal biopsy and was unsuccessfully treated with a gluten-free diet.[10] Other complications associated with LPI include lupus, haemophagocytic lymphohistiocytosis[11] and sudden infant death.[12]

Intestinal biopsies in cases of **congenital chloride diarrhoea** and **congenital sodium diarrhoea** have been normal or show only mild partial villus atrophy.[13] Heubi and colleagues[14] described a severe refractory diarrhoea due to a primary disorder of **bile acid absorption**, but intestinal biopsies were normal. It is worth noting that bile acid-related diarrhoeas more commonly occur secondary to chronic pancreatic insufficiency[15] or to loss of ileal surface (short gut syndrome) due to factors such as necrotizing enterocolitis[16] or extensive ileal resection in Crohn's disease.[17,18]

Lipid trafficking disorders

Most clinical disorders of fat malabsorption result from severe liver disease, pancreatic disease (such as cystic fibrosis), or extensive ileal resection (as in Crohn's disease) with loss of the enterohepatic circulation of bile acids. Intestinal biopsies play a limited role in the diagnosis of secondary fat malabsorption disorders. However, primary abnormalities of fat transport within the enterocyte, though much less frequent, can result in a characteristic vacuolization of the enterocyte in intestinal biopsies. These include abetalipoproteinemia, hypobetalipoproteinemia and chylomicron retention disorder.

Abetalipoproteinemia is an autosomal recessive disorder characterized by the absence of apo B-containing lipoproteins. The molecular basis for the defect is an absence of Microsomal Triglyceride Transfer protein (MTP), responsible for assembly of lipoprotein particles and proper folding of ApoB, preventing its premature degradation.[19] Fatty acids within intestinal cells thus cannot be processed and exported as chylomicrons. Affected patients have diarrhoea and fat malabsorption usually appearing within the first few months of life, with characteristic acanthocytosis resulting from abnormal erythrocyte membranes and deficiencies in fat-soluble vitamins resulting in retinitis pigmentosa and neurologic symptoms. There is clinical heterogeneity, however, with signs and symptoms presenting in older patients in a significant proportion of cases. Serum levels of cholesterol and triglycerides are typically low and do not rise after a fatty meal. Villous morphology is generally preserved. Characteristic fat-filled enterocytes are noted on intestinal biopsies of fasting patients (Figure 1). On electron microscopy these contain fat particles that are irregular in size and generally non-membrane-bound. No lipid is noted in the extracellular space. Hepatic biopsies typically reveal steatosis and occasionally show fibrosis that evolves to cirrhosis.[20] Patients with homozygous ***hypobetalipoproteinemia***, an autosomal dominant disorder