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Chapter 42

Neurologic manifestations of malabsorption syndromes

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INTRODUCTION

Any engine requires fuel to run and the human body is no different. However, fueling the body is not quite as simple as placing the nozzle from the gas pump into the automobile gas tank and pumping in the gasoline. For the human body, the required fuel is complex, and multiple steps are required to ensure that the fuel is converted into usable form and actually is taken into the body. Impaired function at any of these steps can result in failure to properly absorb the fuel. The fuel itself consists of three basic types of nutrients: carbohydrates, fats, and proteins. Intermixed with these three elements are other substances or additives – vitamins and minerals – that are also required by the body to function properly and must be absorbed along with the essential nutrients.

Digestion actually begins in the mouth, where food is chewed and intermixed with salivary enzymes such as amylase. After transfer to the stomach, further mechanical disruption of the food into smaller and smaller particles takes place until the now semi-liquid chyme is ready to be disgorged from the stomach into the duodenum in an orderly fashion, which is controlled by the pyloric sphincter. Particles generally must be smaller than 0.5 mm to be allowed egress from the stomach into the duodenum through the pyloric sphincter (Meyer, 1980). Once in the small intestine, the chyme is exposed to additional enzymes secreted from the pancreas, to bile salts released from the gall bladder, and to still more enzymes found on the brush border membrane and within the mucosal surface of the small intestine itself, all of which promote digestion and ready the nutrients for absorption (Farrell, 2002). The small intestine then continues to mix and propel its contents, with the mixing ensuring maximum exposure of its contents to the intestinal mucosa, where actual absorption occurs. Although the small intestine appears to be tucked into a relatively small compartment of the body, it is actually 22–23 feet long in adults and has an absorptive surface of approximately 300 square yards (250 square meters), which is the approximate size of a tennis court (Insel et al., 2010). This is possible because of the huge number of folds, villi, and microvilli that constitute and markedly expand the absorptive surface.

ABSORPTION AND MALABSORPTION

Absorption of nutrients

A full description of the intricacies of gastrointestinal absorption is beyond the scope of this chapter (and the expertise of this neurologist), but a very brief summary of the mechanisms of absorption of fat, carbohydrate, protein, vitamins, minerals, and trace elements will be undertaken.

Approximately 35% of adult food energy intake consists of lipids, predominantly triglyceride (Pot et al., 2012). Most dietary lipid is absorbed in the jejunum (Borel et al., 1989). Because fat is insoluble in water, intricate mechanisms exist to assist in its absorption. Dietary fat is first broken down into emulsified droplets that are stabilized by coating with phospholipid and then acted upon by lipases, initially in the stomach and then more extensively in the duodenum, which break down triglyceride into fatty acids and monoglyceride. These products of lipolysis then are formed into micelles by bile salts, which then travel to the enterocyte bush border membrane for absorption (Maldonado-Valderrama et al., 2011). Other dietary lipids, such as phospholipids and cholesterol esters, are handled in a slightly different fashion but are also transported to the enterocyte brush membrane in micelles (Farrell, 2002). Within the enterocyte, triglyceride is resynthesized and

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packaged, along with cholesterol and phospholipids, into chylomicrons and very low-density lipoproteins for export into the lymphatic circulation (Thomson et al., 1993). An important component of the surface of chylomicrons is apolipoprotein, which is necessary for both their formation within and secretion from the enterocyte (Ros, 2000).

Carbohydrate accounts for approximately 48% of food energy intake in adults (Whitton et al., 2011). Digestable dietary carbohydrate consists primarily of starch in the form of the polysaccharides amylose and amylopectin, which are made up of long chains of glucose molecules, or of sugars in the form of disaccharides such as lactose and sucrose, or monosaccharides such as fructose and glucose. First salivary amylase and then pancreatic amylase break starch down into short oligosaccharides, such as maltose and maltriose. These oligosaccharides and the dietary disaccharides cannot themselves be absorbed, but are further hydrolyzed to monosaccharides (glucose, fructose, galactose) by hydrolases (e.g., maltase, lactase, sucrase) within the brush border membrane of the enterocytes, where they are then absorbed via saturable carrier-mediated transport systems.

Protein provides approximately 10–15% of energy intake in the average Western diet (Farrell, 2002) and is the primary source of amino acids. It can be derived both from animal and plant sources. Protein digestion is initiated within the stomach by the actions of proteolytic enzymes called pepsins, which break protein down into smaller peptides that are then released into the small intestine. There the peptides encounter pancreatic proteases such as trypsin, chymotrypsin, elastin, and carboxypeptidase A and B, which work together to reduce the peptides further into oligopeptides and individual amino acids. At the brush border membrane there are still more peptidases. Within the brush border there are separate systems for absorbing neutral, basic, and acidic amino acids.

Vitamins can be divided into those that are water-soluble and those that are fat-soluble. Water-soluble vitamins include ascorbic acid (vitamin C), thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pyridoxine (vitamin B_6), cobalamin (vitamin B_{12}), folic acid, pantothenic acid, and biotin. Although in the past it was assumed that most of these substances were absorbed by passive diffusion, it is now recognized that active, carrier-mediated processes are responsible (Said, 2011). Vitamins A, D, E, and K are all polar lipids and thus, are fat-soluble rather than water-soluble. Therefore the initial steps in their digestion probably consist of their transfer from the food matrix in which they are embedded to micelles or perhaps to smaller lipid vesicles (Borel et al., 2001). They are then absorbed in the small intestine, either by passive diffusion (vitamins A, D, E) or by a carrier-mediated process (vitamin K_1) (Farrell, 2002). Intricate systems are present to control and regulate the absorption of minerals and trace elements, which takes place primarily in the small intestine.

Malabsorption

If the stomach is unable to properly carry out its mixing function, either because prior disease has impaired its muscular function or prior surgery, such as gastric resection or bariatric surgery, has diminished its holding capacity, inadequately mixed and osmotically active material may be dumped rapidly into the duodenum. This, in turn, may result in inadequate mixing of bile salts and pancreatic enzymes with the chyme while at the same time the increased osmotic pressure draws additional fluid into the intestine, which increases the bulk of the ingested material and causes it to move rapidly through the intestine, limiting both time and extent of contact of the ingested material with the intestinal mucosa, where absorption would normally occur. The net result of this mad dash of partially digested food through the intestine can be reduced absorption of nutrients and associated diarrhea, the hallmarks of malabsorption.

Malabsorption may also occur via other mechanisms. Impaired micelle formation due to reduced luminal concentrations of bile salts, as a consequence of hepatic or gall bladder dysfunction, can result in fat malabsorption (Van Deest et al., 1968). Pancreatic insufficiency from a variety of causes can result in decreased lipase secretion with consequent fat malabsorption and decreased secretion of trypsin and chymotrypsin with resultant protein malabsorption (Owens and Greenson, 2007). Disease processes affecting the enterocytes can impair both fat absorption and chylomicron formation, with subsequent malabsorption of fat. Poor mixing of gastric and intestinal contents and mucosal disease processes also can impair protein and carbohydrate absorption. Loss or reduction of the absorptive surface, whether due to disease processes or to surgical removal, may also result in malabsorption.

The clinical signs and symptoms of malabsorption classically involve the gastrointestinal system, with abdominal distension, abdominal pain, flatulence, diarrhea, weight loss, and even ascites. However, systemic signs also may appear. Abnormalities of the skin and mucous membranes can become evident, as can musculoskeletal, renal, and hematologic dysfunction.

Neurologic involvement may develop in some malabsorptive disorders and can assume a variety of appearances. It is not possible in this chapter to fully detail all disorders of gastrointestinal absorption that may result in neurologic dysfunction. Some of these disorders are discussed in detail in their own chapters in this

compendium and will be treated lightly here. Others will be discussed more fully, but the disease processes discussed in the following paragraphs might best be considered a sampling of disorders that may be of most interest to the adult neurologist.

NEUROLOGIC DYSFUNCTION IN MALABSORPTION SYNDROMES

The list of congenital disorders of the gastric and intestinal mucosa that result in malabsorption is very long and includes disorders that are characterized by malabsorption of amino acids (e.g., Hartnup disorder, cystinuria, blue diaper syndrome, Lowe's syndrome, oasthouse syndrome, and others), carbohydrates (e.g., lactase deficiency, trehalase deficiency, glucose galactose malabsorption, and others), fat (see below), and also various vitamins and minerals (Högenauer and Hammer, 2002). Many of these present during infancy and not all produce neurologic dysfunction. All cannot be covered here. The following paragraphs will focus on disorders that do produce neurologic dysfunction; both acquired and inherited disorders will be addressed and those that may appear in adult life will be preferentially described.

Vitamin E deficiency

Neurologic dysfunction in the setting of vitamin E deficiency can be genetic in origin, with an autosomal recessive inheritance pattern and a clinical presentation that can mimic Friedreich's ataxia, due to a mutation in the α-tocopherol transfer protein gene (Ben Hamida et al., 1993; Ouahchi et al., 1995; Fogel and Perlman, 2007; Di Donato et al., 2010). In most instances, however, it is the consequence of fat malabsorption (Laplante et al., 1984; Ayuso Blanco et al., 1994). This can occur following both partial and complete gastrectomy (Rino et al., 2007; Ueda et al., 2009), in the setting of primary biliary cirrhosis (Sokol et al., 1989) or other biliary diseases (Ayuso Blanco et al., 1994), in individuals with pancreatic dysfunction (Yokota et al., 1990), in patients with common variable immunodeficiency with associated enteropathy (Aslam et al., 2004; Malamut et al., 2010), in persons with inflammatory bowel disease (Howard et al., 1982; Vorgerd et al., 1996), or with cystic fibrosis (Bye et al., 1985; Willison et al., 1985).

The neurologic symptoms and signs in individuals with vitamin E deficiency can be quite varied. Ataxia is frequently present. Dysarthria and nystagmus may occur. Symptoms and signs of peripheral neuropathy, including paresthesias, impaired proprioception, impaired vibratory perception, and hyporeflexia are also common. Proximal muscle weakness, myopathy, hyperreflexia, extensor plantar responses, pigmentary retinopathy, action tremor, limb dysmetria, and even myoclonic dystonia have also been described (Angelini et al., 2002; Aslam et al., 2004; Hammond and Wang, 2008).

Abnormalities consistent with peripheral neuropathy may be evident on electromyography and nerve conduction studies (EMG/NCV) but are not universally present (Ko and Park-Ko, 1999; Hammond and Wang, 2008). Somatosensory evoked potentials may demonstrate abnormalities indicative of posterior column dysfunction (Puri et al., 2005). Diffuse white matter changes have also been described in individuals with vitamin E deficiency, both in the cerebrum (Aslam et al., 2004) and in the spinal cord (Vorgerd et al., 1996).

The appearance of symptoms of vitamin E deficiency can be strikingly delayed. In patients post gastrectomy, it may take up to 50 months for evidence of vitamin E deficiency to appear (Ueda et al., 2009). The same investigators reported that replacement doses of vitamin E needed to be 300 mg/day or more.

Familial hypocholesterolemia

Three distinct genetic disorders, familial hypobetalipoproteinemia (FHBL), abetalipoproteinemia (ABL), and chylomicron retention disease (CRD), have been identified as causes of chronic diarrhea, malabsorption, malnutrition, growth retardation, and vitamin E deficiency. Of the three, neurologists are most familiar with ABL, previously known as the Bassen–Kornzweig syndrome (Bassen and Kornzweig, 1950; Sturman, 1968), but awareness of the other two is of value.

ABL is an autosomal recessive disorder due to a mutation in the microsomal triglyceride transfer protein (*MTP*) gene on chromosome 4 (Shoulders et al., 1993). MTP acts as a chaperone that transfers lipids such as triglycerides, cholesterol esters and phospholipids onto apolipoprotein B (APOB), thus promoting the secretion of chylomicrons from the enterocytes and very low-density lipoproteins (VLDLs) from hepatocytes (Zamel et al., 2008; Zeissig et al., 2010). Mutations lead to a nonfunctional MTP, with resultant impaired biogenesis of chylomicrons and VLDL and inability to absorb fats and fat-soluble vitamins, perhaps most importantly vitamin E. The clinical features of ABL include steatorrhea, diarrhea, retinitis pigmentosa, acanthocytosis, and a variety of neurologic features; hepatic manifestations due to hepatic steatosis, occasionally leading to cirrhosis, may also be present (Braegger et al., 1998). Blood lipid analysis demonstrates extremely low plasma levels of total cholesterol, VLDL, and low-density lipoproteins (LDL); APOB, triglycerides, and chylomicrons are virtually absent (Stevenson and Hardie, 2001; Palau and Espinós, 2006; Tarugi et al., 2007). Gastrointestinal symptoms are usually evident during infancy,

but neurologic dysfunction may not appear until individuals are in their teens or even later (Fogel and Perlman, 2007). Neurologic dysfunction typically consists of progressive cerebellar ataxia. Peripheral neuropathy may also develop. The neuropathy is sensorimotor (but predominantly sensory) in character and primarily associated with impairment of position and vibratory sensation, along with reduced or absent muscle stretch reflexes; both demyelinating (Wichman et al., 1985) and axonal (Iannaccone and Sokol, 1986) pathology have been described. Both the ataxia and the peripheral neuropathy have most often been attributed to vitamin E deficiency, but investigators describing the demyelinating features of the neuropathy have questioned its relationship to vitamin E deficiency. Additional neurologic abnormalities have been described in individuals with ABL. Upper motor neuron signs, such as hyperreflexia and Babinski signs, have been reported (Zamel et al., 2008), as have resting and postural tremor (Soejima et al., 2006). Treatment of neurologic dysfunction with both vitamin E and vitamin A has been advocated, but results have been mixed (Grant and Berson, 2001; Zamel et al., 2008).

In contrast to ABL, FHBL is an autosomal codominant disorder in which heterozygotes may have mild symptoms or be asymptomatic except for low plasma cholesterol, whereas homozygotes may be clinically indistinguishable from individuals with ABL (Noto et al., 2009; Peretti et al., 2010). In approximately 50% of individuals, FHBL is due to a mutation in the *APOB* gene, which is on chromosome 2 (Whitfield et al., 2003; Tarugi et al., 2007). This results in the formation of a truncated APOB protein. The lipid profile of individuals with homozygous FHBL is similar to that of individuals with ABL; in contrast, heterozygotes have reduced but not absent total cholesterol, triglyceride, LDL, and APOB levels and high-density lipoproteins (HDL) may actually be elevated (Linton et al., 1993; Peretti et al., 2010). Homozygous individuals frequently develop retinitis pigmentosa and virtually always have acanthocytosis; neurologic dysfunction is similar to that present in ABL, but may be somewhat less severe (Linton et al., 1993). Neurologic dysfunction is unusual in heterozygotes.

CRD (also called Anderson's disease) is a very rare autosomal recessive disorder due to mutation in the *SAR1B* gene on chromosome 5, which encodes the SAR1B protein (Georges et al., 2011). SAR1B is involved with the transport of prechylomicron transport vesicles from the endoplasmic reticulum to the Golgi apparatus in enterocytes; impaired function of the protein results in failure to release chylomicrons following a fat-containing meal and the accumulation of lipids within the enterocytes (Shoulders et al., 2004; Tarugi et al., 2007; Peretti et al., 2010). In CRD, total cholesterol, LDL, HDL, and APOB are all reduced, but triglycerides are normal. Gastrointestinal dysfunction is evident during infancy, but neurologic dysfunction typically does not appear until the teenage years or adulthood (Peretti et al., 2010). Symptoms suggestive of a peripheral polyneuropathy are the most common neurologic presentation (Peretti et al., 2009), but in adults ataxia, myopathy, and action tremor have all been described (Gauthier and Sniderman, 1983; Peretti et al., 2010). Vitamin E deficiency is the presumed etiology for the neurologic deficits; Peretti et al. (2010) noted that individuals with the more pronounced abnormalities had the lowest vitamin E levels at the time of diagnosis. Treatment with vitamins E, A, and D are recommended to prevent neurologic, ophthalmologic, and osteopenic complications of CRD (Gauthier and Sniderman, 1983; Peretti et al., 2010).

Celiac disease

The topic of gluten sensitivity is covered extensively in another chapter in this volume. Celiac disease (CD) will be covered briefly here to emphasize that patients with the classic gastrointestinal symptoms and pathology of CD may also develop neurologic dysfunction. However, it is not at all certain that the neurologic abnormalities of classic CD are the result of malabsorption; immunologic mechanisms may be a more probable explanation (Bürk et al., 2009).

The prevalence of CD, at least in American and European populations, has been estimated to be approximately 1% (Green and Cellier, 2007; Tjon et al., 2010), but recent studies suggest that the number of undiagnosed patients may be considerable and the prevalence much higher than previously proposed (Vilppula et al., 2008). The classic gastrointestinal symptoms of CD primarily are due to fat malabsorption and consist of diarrhea, weight loss, and gassy distension that develop as a consequence of damage to the mucosa of the small intestine, triggered by an immune-mediated response to gluten, the protein fraction of wheat. Malabsorption develops as a consequence of the mucosal injury, which results in blunting and atrophy of the villi, along with crypt hyperplasia. Individuals with classic CD display the presence antigliadin antibodies, both IgG and IgA. They also display the presence of additional gliadin-related antibodies, such as antiendomysial and antitransglutaminase antibodies.

Neurologic dysfunction has been reported to develop in 6–12% of individuals with CD (Pellecchia et al., 1999; Lagerqvist et al., 2001; Vaknin et al., 2004). A broad array of neurologic manifestations has been described, including peripheral neuropathy (Chin et al., 2003;

Briani et al., 2005; Bushara, 2005), myopathy (Uygur-Bayramicli and Ozel, 2011), epilepsy (Bushara, 2005), myelopathy (Cooke and Smith, 1966), neuromyelitis optica (Jacob et al., 2005), headache (Cicarelli et al., 2003; Morello et al., 2003; Bushara, 2005), restless legs (Manchanda et al., 2009; Weinstock et al., 2010; Uygur-Bayramicli and Ozel, 2011), acute inflammatory demyelinating neuropathy (Midha et al., 2007; Gupta and Kohli, 2010), chorea (Pereira et al., 2004), paroxysmal nonkinesigenic dystonia (Hall et al., 2007), autonomic imbalance (Barbato et al., 2010), and others. Some of the reports may simply reflect coincidence and in most of the others no clear connection to malabsorption has been suggested. The two neurologic disorders described most often in the setting of celiac disease are ataxia and peripheral neuropathy. With regard to peripheral neuropathy, one review of the existing literature prompted a conclusion that an association of celiac disease and peripheral neuropathy is unlikely and that celiac disease should not be considered in the workup of patients with chronic peripheral neuropathy (Rosenberg and Vermeulen, 2005).

Tropical sprue

Tropical malabsorption is a syndrome that may affect both indigenous residents of tropical countries and travelers visiting or residing in the tropics (Ramakrishna et al., 2006). Both secondary forms, in which an etiology has been identified, and primary (idiopathic) forms have been described. Small intestine mucosal damage inflicted by protozoa (e.g., *Giardia intestinalis*, *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis*), helminths (e.g., *Strongyloides stercoralis*, *Capillaria philippinensis*), bacteria (e.g., *Mycobacterium tuberculosis*) and viruses (possibly human immunodeficiency virus) may all produce a malabsorption syndrome, as can a variety of other disease processes of inflammatory, autoimmune, neoplastic, or pancreatic origin (Ramakrishna et al., 2006).

It is in individuals in whom no etiology can be ascertained that the name tropical sprue (TS) has been applied. Although currently infrequently encountered in North America, TS has been reported to account for approximately 40% of malabsorption in children and adults in some portions of South Asia (Ranjan et al., 2004), although others have found it to be a rare cause of small bowel diarrhea (Thakur et al., 2006). Gastrointestinal symptoms of TS include chronic nonbloody diarrhea, bloating, weight loss, and abdominal cramping (Batheja et al., 2010). The mucosal changes in tropical sprue are sometimes indistinguishable from those of CD, although TS typically involves the entire length of the small intestine, whereas CD typically spares the terminal ileum (Batheja et al., 2010). The mucosal damage in TS results in malabsorption of fat, carbohydrates, and multiple vitamins, including folate and vitamins A, E, and B_{12} (Ramirez et al., 1973; Glynn, 1986; Ramakrishna et al., 2006).

Neurologic dysfunction may develop in the setting of TS. In one study, neurologic symptoms were documented in 67% (16/24) of individuals with TS (Iyer et al., 1973). In this study, proximal muscle weakness was present in 15 of the 16 individuals with neurologic symptoms, but on electrophysiologic testing only 10 had evidence of myopathy; peripheral neuropathy was noted in eight. Night blindness, presumably due to vitamin A deficiency, and combined system degeneration, presumably the result of vitamin B_{12} deficiency, have been described in TS (Ramakrishna et al., 2006). Peripheral neuropathy in patients with TS has been attributed to vitamin E deficiency (Ghalaut et al., 1995). Periodic paralysis has been reported in an individual with TS (Ghosh et al., 1994).

Antibiotic therapy, typically with tetracycline or doxycycline for several months, and vitamin replacement therapy are the standard treatments for TS, but abnormal small intestine permeability may remain evident following treatment and some stool frequency and weight loss may persist (Kumar et al., 2011).

Wernicke's encephalopathy

Neurologists are well acquainted with Wernicke's encephalopathy (WE) in the setting of chronic alcoholism with nutritional thiamine deficiency, but it can also be the result of malabsorption of thiamine. Considering the possibility of WE in patients who are not alcoholics can be especially problematic since the full classic triad of neurologic features of WE, mental status changes, ophthalmoplegia (nystagmus is actually more common than ophthalmoplegia), and gait ataxia, develops in only 10–16% of affected individuals (Harper et al., 1986; Weathers and Lewis, 2009).

Thiamine is primarily absorbed in the duodenum, but the stomach may also play a role (Uruha et al., 2011). In keeping with this, the development of WE in a patient with peptic ulcer disease was attributed to gastric malabsorption of thiamine due to severe gastric mucosal lesions (Uruha et al., 2011). WE has also been documented following bariatric surgery, including techniques such as Roux-en-Y gastric bypass, vertical banded gastroplasty, and gastric partitioning (Rothrock and Smith, 1981; Seehra et al., 1996; Cirignotta et al., 2000; Salas-Salvadó et al., 2000; Toth and Voll, 2001; Koffman et al., 2006; Singh and Kumar, 2007). It may develop anywhere between 2 and 78 weeks following surgery, although 4–12 weeks

postoperatively is the most frequent timeframe (Singh and Kumar, 2007). In a recent review, Aasheim (2008) catalogued 84 cases of WE following bariatric surgery; in 95%, gastric bypass or a restrictive procedure had been performed. The appearance of WE is more frequent in individuals who experience repeated vomiting, presumably with decreased thiamine absorption because of the vomiting (Cirignotta et al., 2000; Aasheim, 2008). However, individuals undergoing Roux-en-Y gastric bypass have an additional risk with regard to thiamine, since thiamine is predominantly absorbed in the duodenum, which is bypassed in the Roux-en-Y procedure (Escalona et al., 2004; Al-Fahad et al., 2006; Iannelli et al., 2010).

We has also been described in individuals with other causes for malabsorption. In one woman with a history of premature birth and neonatal necrotizing enterocolitis with subsequent bowel resection, WE developed during pregnancy and was attributed to longstanding chronic malabsorption exacerbated by her pregnancy (Williams et al., 2009). Another individual with colon cancer and an enterocutaneous fistula developed WE following administration of 5-fluorouracil; the role of malabsorption in this patient is uncertain (Papila et al., 2010). Either malabsorption or consumption by the tumor was considered to be responsible for the development of WE in a terminally ill cancer patient who was maintaining a reasonable caloric intake (Yae et al., 2005). WE has also been reported in the setting of pancreatic encephalopathy, but in these cases prolonged fasting and inadequate thiamine supplementation were deemed responsible (Zhang and Tian, 2007).

Pellagra

Pellagra is a disease that is often considered to have died out in the US and other developed countries; however, although rare, it still occurs (Ishii and Nishihara, 1981; Weathers and Lewis, 2009). Pellagra is due to niacin deficiency, although it can also develop in the setting of deficiency of the essential amino acid tryptophan, which is a precursor of niacin (Lanska, 2010). As with WE, pellagra is most often diagnosed in individuals with chronic alcoholism and inadequate nutritional intake, but it can also develop in other conditions, including malabsorption syndromes.

The classic clinical features of pellagra consist of the triad of dermatitis, diarrhea, and dementia. All three are not present in every individual; in one study the entire triad was present in only 22% (Spivak and Jackson, 1977). In addition to dementia, neurologic abnormalities that have been described in pellagra include headache, vertigo, myoclonus, tremor, rigidity, weakness, dysphagia, seizures, and still others; a variety of psychiatric symptoms may also be evident (Serdaru et al., 1988; Weathers and Lewis, 2009).

Pellagra has been documented in individuals with malabsorption due to a variety of causes. Several case reports describe the development of pellagra in people with Crohn's disease, in which both niacin deficiency due to malabsorption and tryptophan wastage with increased urinary excretion of 5-hydroxyindoleacetic acid have been suggested to occur (Pollack et al., 1982; Zaki and Millard, 1995; Abu-Qurshin et al., 1997). Pellagra has been reported in an immunocompromised patient with colitis due to cytomegalovirus (Lu et al., 2001). Small intestinal bacterial overgrowth with consequent malabsorption and development of pellagra has also been described (Wierzbicka et al., 2005). Malabsorption secondary to amyloidosis in an individual with multiple myeloma is yet another reported cause of pellagra (Itami et al., 1997).

Copper deficiency myelopathy

Copper is an essential trace metal and micronutrient that is important for many biological functions (Stern, 2010; de Romaña et al., 2011). It is incorporated into at least 30 metalloenzymes and involved with catecholamine synthesis, brain peptide synthesis, oxidative defenses, and numerous other metabolic processes (Tapiero et al., 2003; Zara et al., 2009). Neurologists are most familiar with the damage that can be caused by excessive copper, as in Wilson's disease, but copper deficiency also produces neurologic dysfunction. This is, perhaps, best recognized in Menkes disease, in which there is a genetically based inability to transport copper across the intestinal barrier due to a mutation in the *ATP7A* gene (de Bie et al., 2007; Tümer and Møller, 2010; Kodama et al., 2011). However, impairment of intestinal copper absorption may also occur in the setting of other malabsorptive processes.

Copper, along with zinc, is absorbed in the proximal small intestine, primarily in the duodenum but also to a lesser extent in the stomach and more distal small intestine (Mason, 1979; Tan et al., 2006). Processes that remove these sites or otherwise impair absorption from them result in eventual copper deficiency. However, it is only within the past decade that neurologic dysfunction as a consequence of copper deficiency due to copper malabsorption has been identified in individuals who had previously undergone gastric and/or intestinal surgery (Schleper and Stuerenburg, 2001; Kumar et al., 2003b; Kumar, 2006; Tan et al., 2006; Bellance et al., 2010; Jaiser and Winston, 2010; Pineles et al., 2010).

Schleper and Stuerenburg (2001) described a 46-year-old woman who developed progressive spastic tetraparesis, sensory impairment, and sensory gait ataxia and

was subsequently diagnosed with copper deficiency-associated myelopathy. She had undergone partial gastrectomy approximately 20 years earlier for treatment of gastric ulcers and a second gastric resection procedure along with resection of the transverse colon approximately 5 years earlier because of complications from the original procedure. Serum copper and ceruloplasmin levels were markedly diminished; cerebrospinal fluid copper was also diminished, excluding a diagnosis of Wilson's disease (24 hour urinary copper was not reported). Kumar et al. (2003b) subsequently described two individuals, again both women, who also developed progressive myelopathy and sensory gait ataxia following gastrointestinal surgical procedures. The first woman had undergone an intestinal bypass procedure for obesity 24 years previously; the second woman had undergone two procedures, partial small bowel resection for Crohn's disease 30 years previously and partial gastrectomy and vagotomy for refractory ulcers 15 years previously. In both individuals, serum copper and ceruloplasmin levels were markedly reduced and 24 hour urinary copper excretion was normal. Kumar (2006) subsequently reviewed the case records of 25 persons who were diagnosed with copper deficiency myelopathy (CDM); 10 of them had a history of prior gastric surgery. More recently, Jaiser and Winston (2010) reviewed 55 case reports of copper deficiency myelopathy collected from the literature and confirmed prior upper gastrointestinal surgery as an important (though not the only) risk factor. They noted a striking female predominance (F:M = 3.6:1) and attributed the copper deficiency to impaired absorption in the upper gastrointestinal tract.

Although prior gastric or intestinal surgery may be the most frequent cause of CDM, it has also been reported in individuals with excessive zinc ingestion (Kumar et al., 2003a) and in individuals with other reasons for malabsorption, such as celiac disease (Kumar and Low, 2004; Kumar, 2006; Jung and Marziniak, 2008; Jaiser and Winston, 2010).

The clinical features of CDM closely mimic those of subacute combined degeneration due to vitamin B_{12} deficiency (Kumar et al., 2004). The combination of posterior column dysfunction with sensory ataxia and associated corticospinal tract dysfunction are common to both; peripheral neuropathy may also be present in both, although it is not a predominant feature of CDM. Hematologic manifestations are frequently, though not invariably, present in both; anemia and neutropenia are characteristic in CDM and the anemia may be microcytic, macrocytic, or normocytic (Kumar, 2006). Although myelopathy, often with associated peripheral neuropathy, is the most frequent clinical presentation of CDM, optic neuropathy may also be part of the clinical picture (Spinazzi et al., 2007; Pineles et al., 2010). Neuroradiologic changes, most typically in the form of increased T2 signal activity within the dorsal columns in the cervical cord, are often present in both CDM and subacute combined degeneration (Kumar et al., 2006).

The response to copper replacement therapy in CDM is inconsistent. Although the hematologic abnormalities typically respond promptly, neurologic dysfunction does not always do so. Progression of dysfunction is often halted, but resolution of neurologic dysfunction is often incomplete (Kumar, 2006).

Whipple's disease

Whipple's disease (WhD) is an example of a disease process in which, although characterized by both gastrointestinal malabsorption and neurologic dysfunction, the neurologic dysfunction is not the result of malabsorption but rather due to central nervous system involvement of the primary disease process itself. Nevertheless, it will be briefly detailed here because of the presence of both malabsorption and neurologic dysfunction.

Although originally described as a gastrointestinal disease, it has become abundantly clear that WhD is a multisystem disorder that may also demonstrate joint, dermatologic, lymphatic, cardiac, pulmonary, ocular, and neurologic dysfunction (Dutly and Altwegg, 2001). Thus, in addition to diarrhea, weight loss, and abdominal pain, individuals with WhD may display migratory polyarthritis, generalized lymphadenopathy, anemia, fever, generalized malaise, chronic cough, pseudo-addisonian skin pigmentation, congestive heart failure, hypotension, pericardial friction rub, splenomegaly, focal glomerulitis, visual changes, uveitis, retinitis, and a variety of neurologic manifestations (Weiner and Utsinger, 1986; Dutly and Altwegg, 2001; Ojeda et al., 2010).

The average age of symptom onset in WhD is approximately 50 years. Males are affected much more frequently than females; in the past the male-to-female ratio was 8:1 but in recent years this may have dropped to 4–5:1 (Dutly and Altwegg, 2001). Farmers have an increased risk for developing WhD (Weiner and Utsinger, 1986). The organism responsible for WhD, *Tropheryma whipplei*, has been identified and characterized as a member of the actinomycete family; it has been suggested that *Tropheryma whipplei* may be a soil-dwelling organism, which might explain the increased incidence of infection in farmers (Dutly and Altwegg, 2001). It has also been found in the influxes to sewage plants, particularly those from agricultural communities (Schöniger-Hekele et al., 2007; Schneider et al., 2008).

Neurologic dysfunction may be the presenting feature in approximately 5% of persons with WhD (Peters et al., 2002). Clinical central nervous system involvement

eventually develops in 10–43% of patients with WhD; postmortem examinations demonstrate central nervous system lesions in over 90% of both symptomatic and asymptomatic individuals (Dutly and Altwegg, 2001; Peters et al., 2002). Cognitive changes appear in 71% of individuals; and may be accompanied by psychiatric symptoms such as depression and personality or behavioral changes (Louis et al., 1996; Franca et al., 2004). Insomnia, hypersomnia, hyperphagia, polyuria, and polydipsia are uncommon, but do occur (Louis et al., 1996; Perkin and Murray-Lyon, 1998; Dutly and Altwegg, 2001). Cerebellar dysfunction with gait and balance impairment and pyramidal tract abnormalities may also develop (Louis et al., 1996; Franca et al., 2004). A variety of ocular and extraocular abnormalities, such as vertical gaze impairment, extraocular muscle dysfunction, internuclear ophthalmoplegia, ptosis, and pupillary abnormalities may also occur (Chan et al., 2001; Franca et al., 2004). Oculomasticatory myorhythmia, consisting of the combination of pendular convergence nystagmus and concurrent slow, rhythmic synchronous contractions of the masticatory muscles, invariably accompanied by a supranuclear vertical gaze paresis, develops in approximately 20% of individuals with central nervous system involvement (Schwartz et al., 1986; Louis et al., 1996). Peripheral neuropathy is a neurologic feature of WhD that actually may be the direct result of nutritional deficiency due to malabsorption (Topper et al., 2002; Franca et al., 2004).

PCR analysis appears to be a more sensitive method of diagnosis than identification of PAS-positive inclusions in macrophages present in duodenal biopsy specimens, but there is some evidence that *Tropheryma whipplei* DNA may be present in healthy individuals without WhD (Dutly and Altwegg, 2001; Peters et al., 2002). In individuals with central nervous system symptomatology, brain biopsy is positive over 80% of the time; cerebrospinal fluid analysis, including PCR, may also be useful (Louis et al., 1996; Perkin and Murray-Lyon, 1998; Schijf et al., 2008).

Prompt diagnosis of WhD is important because effective treatment is available. An initial 2 week course of parenteral therapy with either a combination of penicillin G and streptomycin or with a third generation cephalosporin (e.g., ceftriaxone), followed by a 1 year course of oral trimethoprim-sulfamethoxazole has been recommended as an effective treatment approach (Dutly and Altwegg, 2001). The prolonged course of trimethoprim-sulfamethoxazole is considered by some to be important to prevent central nervous system relapses, which have a poor prognosis and high mortality rate, but not all investigators agree that this is the optimum treatment approach and instead recommend a combination of doxycycline and hydroxychloroquine, supplemented by sulfadiazine in patients with neurologic involvement (Lagier et al., 2010).

CONCLUSION

Gastrointestinal diseases resulting in malabsorption and consequent nutritional deficiencies can be accompanied by neurologic dysfunction that can manifest itself in a broad and confusing array of symptoms and signs. It is important for internists and gastroenterologists to be aware of this possibility and equally important for neurologists to think about the possibility of underlying nutritional deficiency due to malabsorption when evaluating patients for neurologic dysfunction. Prompt and appropriate testing can lead to diagnosis and treatment, which may, at a minimum, forestall further neurologic progression and, in the best of circumstances, result in complete neurologic recovery.

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