

Neuropathy and the Gastrointestinal System

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“Everything is connected...no one thing can change by itself.” Paul Hawken

I. Introduction

Neuropathy related to the gastrointestinal system has most commonly been recognized to result from nutritional deficiencies. These deficiencies could be due to malnutrition (e.g. alcoholism) or a reduced absorptive surface as a result of physical alteration (e.g. surgical resection/bypass) or intestinal wall infiltration (e.g. Crohn's disease). Immune-mediated mechanisms are suspected to play a role in the development of PN in some gastrointestinal conditions now recognized to have multisystemic manifestations (e.g. celiac disease, inflammatory bowel disease).

II. Vitamin and nutritional deficiencies

From the beriberi epidemics of the 19th century due to the mass production of polished, nutrient-poor rice, to the conditions of World War II and Cuba following the collapse of the Soviet Union, large scale human tragedy has often been the catalyst for advances in our understanding of neuropathy due to nutritional deficiencies. Prolonged parenteral nutrition, eating disorders, alcohol abuse, physiological states (e.g. pregnancy), and certain medications (e.g. isoniazid or penicillamine which are pyridoxine antagonists) have been also recognized to result in a deficiency state.

The typical features of neuropathies associated with particular nutritional derangements are summarized in Table 1.0; however, it is likely that multiple vitamin deficiencies, rather an isolated single vitamin deficiency, may be the cause of most presentations (Victor, 1983).

Vitamin B1 (thiamine) deficiency. (For more details about neuropathy from thiamine deficiency, see “Alcoholic neuropathy” section.) Controversy remains about the best way to diagnose this deficiency. Indirect measurements include measurement of erythrocyte transketolase activity, which is reduced in a deficiency state. The transketolase activity normalizes rapidly following dietary supplementation, making the test a less practical and reliable indicator of chronic thiamine deficiency. Measurement of enhancement of enzymatic activity from added thiamine diphosphate (TPP) is an additional method of determining thiamine deficiency. If activity is increased >15% by added TPP, a deficiency state is probably present. Beginning in the 1980s, thiamine concentrations could be measured by high-performance liquid chromatography (normal=20-50 ng/ml). The reliability and consistency of these measurements are debatable (Shields, 2002; Koike et al, 2001a).

Vitamin B6 (pyridoxine). Pyridoxine deficiency most often occurs in the context of general malnutrition, as in the case of alcoholism, or due to medications such as isoniazid and hydralazine, which are pyridoxine antagonists. Neuropathy related to pyridoxine *excess* has been reported in patients taking 200-2000 mg/day (Perry et al, 2004; Schaumburg et al, 1983). This particular neuropathy has served as a useful model for studying the pathogenesis and treatment of PN. HSV-mediated gene transfer of neurotrophin-3 and nerve growth factor prevented degeneration of large myelinated fibers in a pyridoxine neuropathy model in rats (Chattopadhyay et al, 2003; Chattopadhyay et al, 2005). A benefit from 4-methylcatechol (Callizot et al, 2001) and glutamate (Arkaravichien et al, 2003) has also been described.

Vitamin B12 (cobalamin) deficiency. Cobalamin absorption is a complex, multistep process that requires peptic digestion, R-protein (a cobalophilin secreted by the salivary glands), pancreatic enzymes in an alkaline milieu, and intrinsic factor. Megaloblastic anemia is not invariably present in those with prominent neurological manifestations. Additional serum assays, particularly methylmalonic acid (MMA), which is more specific and sensitive than homocysteine, may be useful in the diagnosis (Chaudhry et al, 2002).

III. Alcoholic neuropathy

Alcoholic neuropathy typically presents as a generalized sensorimotor polyneuropathy with numbness, weakness and sensory ataxia. Other reported PN phenotypes include a painful small fiber neuropathy and an acute axonal neuropathy mimicking a Guillain-Barré syndrome (Wohrle et al, 1998). On physical exam, atrophic and “shiny” legs, loss of vibration and deep sensation in distal legs, motor weakness, areflexia, calf tenderness, and orthostatic hypotension due to autonomic neuropathy may be detected (Montforte et al, 1995). Electrodiagnostic abnormalities, described in 67% of chronic alcoholics, are predominantly axonal (Ammendola et al, 2001). Distally-accentuated axonal degeneration involving both myelinated and unmyelinated fibers is the main pathologic feature.

The pathogenesis of alcoholic neuropathy is complex and probably multifactorial. Determining the effects of nutritional and vitamin deficiencies versus the direct toxicity of alcohol itself has been difficult given limitations in adequately assessing for nutritional deficiencies and the fact that abstinence is usually associated with improved food intake and nutritional status.

Evidence supporting a nutritional cause for alcoholic neuropathy is the finding that alcohol diminishes thiamine absorption in the intestine and reduces hepatic thiamine storage. Decreased phosphorylation of thiamine results in the reduction of the active form of thiamine (Shields, 2002). Two frequently cited clinical studies reported that alcoholic PN improved following adherence to a nutritious diet (Strauss, 1935) or the addition of thiamine to a nutritious diet (Victor and Adams, 1961), despite continued heavy alcohol consumption. Furthermore, experimental models of alcoholic PN have not

provided convincing evidence that alcohol acts as a toxin on peripheral nerves (Hallett et al, 1987; Windebank, 1993).

A role for toxicity of alcohol has been based on clinical studies that found a significant correlation between PN and the total lifetime amount of alcohol consumption and the duration of alcohol abuse (Montforte et al, 1995; Vittadini et al, 2001).

Alcoholic neuropathy vs. thiamine-deficiency neuropathy

Initially thought to be indistinguishable, alcoholic neuropathy and thiamine-deficiency neuropathy are reported to exhibit some distinct clinical characteristics. Patients with alcoholic neuropathy [ALN] (defined to be regular intake of >100 grams of ethanol daily for at least 10 years before the onset of neuropathic symptoms) and normal thiamine levels were found to have slowly progressive, painful, predominantly sensory symptoms with relatively selective small-fiber loss (particularly in those with a short duration of symptoms) and relative sparing of deep tendon reflexes. Autonomic symptoms were less frequent and pathologic findings of myelin irregularity and segmental de/remyelination were more common in this group when compared with the thiamine-deficient (TD) neuropathy group. In the TD group, PN developed due to dietary imbalance or prior gastrointestinal surgery, and the patients were found to have acutely progressive, motor-dominant symptoms with impairment of superficial and deep sensation, predominantly large fiber axonal loss, increased autonomic symptoms and less pain. Patients with alcoholic neuropathy *and* thiamine deficiency had characteristics of both the ALN and TD groups (Koike et al, 2003).

Treatment

Abstinence and institution of a nutritious diet are the obvious cornerstones of therapy of alcohol-related PN. There is a case report of one man with decompensated alcoholic liver disease and moderately severe PN, who regained almost normal muscle strength with recovery of sensory and motor conduction velocities, following liver transplantation (Gane et al, 2004).

IV. Gastric surgery

Gastric surgery for weight loss, malignancy, or ulcers is an obvious potential cause for malabsorption or limited absorption resulting in nutritional deficiency-related neuropathies. For patients with neuropathy following gastric surgery who lack clear evidence of malnutrition, the disease mechanism has yet to be determined.

Bariatric surgery (BS)

In the rapidly 'expanding' U.S. population, bariatric surgery is a tantalizing, increasingly pursued means of weight control, particularly in the morbidly obese (body mass index [BMI] > 40 kg/m², or BMI=35-39.9 kg/m² with accompanying co-morbidity). Reversal of the metabolic syndrome of hypertension and elevated lipids and glucose levels is also anticipated following successful weight loss (Koffman et al, 2005). An estimated 140,000 bariatric procedures were performed in 2004 in the U.S. with hospital revenues of \$1-2 billion.

Bariatric procedures can be divided into two categories:

A. Bypass procedures

Jejunioileal bypass procedures, developed in the 1970s, resulted in intolerable side effects, and have generally been abandoned in favor of the NIH-approved Roux-en-Y gastric bypass (RYGBP). Patients are expected to lose 50-70% of their *excess* weight in 12-18 months of RYGBP. For the "super" obese, other procedures producing selective maldigestion and malabsorption have been advocated. Duodenal switch is a procedure involving gastric reduction (with preservation of the duodenal outlet) combined with intestinal bypass/biliopancreatic diversion, resulting in limited nutrient exposure to the distal ileum. Loss of 60-80% of excess weight is expected over a two-year period.

B. Restrictive procedures

Adjustable gastric banding (Lap-Band[®]) is a less invasive (and possibly less effective) procedure that has been available for the last ten years. Vertical banded gastroplasty is a less commonly performed restrictive procedure.

Complications

Acute complications following BS include rhabdomyolysis or immobilization hypercalcemia. Long term complications may include anemia or metabolic bone disease due to vitamin D deficiency with secondary hyperparathyroidism. Nutritional complications following BS may occur for a variety of reasons including: reduced dietary intake, reduced gastric acid, inadequate intrinsic factor secretion, or lack of nutrient exposure to the duodenum (Mason et al, 2005).

Neurologic complications following BS are reported to occur in 0.08-16% of patients according to a review of 18 surgical series reported between 1976-2004. A 4% neurologic complication rate was reported in a single prospective study. In a review of 96 patients (50 case reports), the most common presentations were peripheral neuropathy

in 60 (62%) and encephalopathy in 30 (31%). Of the 60 patients with PN, 40 (67%) had a polyneuropathy and 18 (30%) had mononeuropathies, which included 17 with meralgia paresthetica and one with foot drop (Koffman et al, 2005).

Acute postgastric reduction surgery (APGARS) neuropathy is a term that has been used to describe neuropathy occurring in patients after a period of progressive vomiting, weakness and hyporeflexia. Pain, numbness, incontinence and impairment of vision, hearing, attention, and memory may occur. Patients were found to have gaze-evoked nystagmus, severe proximal symmetric lower extremity weakness, and hyporeflexia with electrodiagnostic studies revealing an axonal sensorimotor polyneuropathy (Akhthar et al, 2002). The incidence in one survey of surgeons was estimated to be about 5.9 cases per 10,000 operations (Chang et al, 2004). The validity of this term as a distinct entity has been disputed as it may overlap with syndromes caused by nutritional deficiencies.

In the only available controlled retrospective study, 435 patients who had BS were compared with 123 patients who had undergone cholecystectomy. Of the patients who underwent BS, 71 (16%) developed PN vs. 3% of the patients who had undergone cholecystectomy. Twenty-seven of the 71 patients had a sensory predominant polyneuropathy with prickling or “dead”-type numbness in the feet and hands, with 16/27 reporting pain (aching, stabbing, burning), 12/27 reporting autonomic symptoms (lightheadedness, urinary incontinence, impotence, constipation), and 9/27 reporting weakness. Thirty-nine of the 71 patients had mononeuropathies (31 median, 2 ulnar, 2 peroneal, 4 other). Five of the 71 patients had radiculoplexus neuropathy with acute asymmetric pain followed by weakness (lower limbs in 3; upper limbs in 2). Those with mononeuropathy and radiculoplexus neuropathy were more likely to have diabetes mellitus. Sural nerve biopsy revealed prominent axonal degeneration and perivascular inflammation. Treatment of the neuropathies was not specifically addressed. Risk factors for developing peripheral neuropathy included: prolonged gastrointestinal symptoms (nausea and vomiting), rapid weight loss, poor follow-up at a nutritional clinic, reduced serum albumin and transferrin levels, post-surgical complications, and jejunoileal bypass (Thaisethawatkul et al 2004).

Pathogenesis

Nutritional deficiencies are suspected to play an important role in the pathogenesis of PN (particularly the sensory-predominant polyneuropathies) following BS (Thaisethawatkul et al, 2004); however, the etiology is probably multifactorial. Other neurologic complications following BS have been linked to the following specific deficiencies.

1. Vitamin B1 (thiamine): Wernicke encephalopathy has been reported to occur within 2-3 months of BS, preceded by persistent vomiting and rapid weight loss (0.11-0.54 kg/day) [Cirignotta et al, 2005; Chaves et al, 2002]. Cognitive symptoms often improve to a greater extent than motor or sensory symptoms following parenteral thiamine therapy (Cirignotta et al, 2005). The deficiency may occur despite dietetic supervision and multivitamin supplementation (Chaves et al, 2002).
2. Vitamin A: Night blindness, xerophthalmia, Bitot spots and anemia have been described following biliopancreatic diversion (Hatzifotis et al, 2003).

3. Copper: A copper deficiency myelopathy clinically similar to subacute combined degeneration (with prominent sensory ataxia due to dorsal column dysfunction) was described in 13 patients (Kumar et al, 2004). All had a varying degree of axonal neuropathy; however, the peripheral nervous system involvement was not the predominant reason for the sensory ataxia in any patient. Four of 13 had a history of gastric surgery, and 1/4 of these patients had intestinal bypass for obesity. In this one patient, reduced copper and ceruloplasmin levels and a normal zinc level were detected. Improvement of sensory symptoms was reported following parenteral copper administration (Kumar et al, 2003).

Other gastric surgery

Gastric surgery for duodenal ulcers or malignancies may also result in neurologic complications due to thiamine deficiency (Nakagawa et al, 2004; Koike et al, 2001a), vitamin E deficiency (Ueda et al, 2005), or copper deficiency (Kumar et al, 2004). Thiamine deficiency postgastrectomy has been described to be identical to beriberi neuropathy with a similar spectrum of clinicopathologic features and substantial recovery (particularly of motor function) following supplementation (Koike et al, 2001a; Koike et al, 2004).

V. Inflammatory bowel disease (IBD)

IBD refers to a group of chronic, recurrent intestinal disorders, which are represented mainly by Crohn's disease and ulcerative colitis (UC). The extraintestinal manifestations of Crohn's disease and UC are diverse. The overall incidence of neurologic complications has been reported to range from 0.2-19.3% (Elsehety and Bertorini, 1997; Gendelman et al, 1982; Lossos et al, 1995) with the incidence of PN varying from 0.9-3.6% in the two largest retrospective series (Lossos et al, 1995; Elsehety and Bertorini, 1997).

The clinical and electrodiagnostic features of 33 patients with IBD (18 with Crohn's and 15 with UC) were described in the largest case series to date of PN in IBD (Gondim et al, 2005). (See Table 2.0.) The patients were categorized into three PN phenotypes with some significant differences noted between the groups. The variety of PN phenotypes probably reflected ascertainment at different stages of IBD evolution and the complex interaction between a variety of IBD effects on the nervous system (i.e. extra-intestinal inflammation, immune-mediated disorder, nutritional imbalances or drug-induced changes).

Patients with small and large fiber sensory axonal PN had a shorter interval duration between IBD and neuropathy compared with those with large fiber sensorimotor PN. Onset of demyelinating PN in relation to IBD was variable. Only 6/33 patients had metronidazole exposure. No clear relationship between the exposure and neuropathy onset was detected and neuropathy symptoms progressed despite discontinuation of the medication.

Fifty-six percent of Crohn's disease patients and 67% of the UC patients received immunomodulatory therapy at some point during the disease course. All the patients in either group who had demyelinating PN had moderate or major improvement in response to immune therapies. Even patients with axonal neuropathies in whom the response could be adequately evaluated (5 Crohn's; 5 UC) typically had a beneficial response (graded mild to moderate).

Table 2.0

	Crohn's disease (N=18)	Ulcerative colitis (N=15)
Neuropathy phenotype		
1. Demyelinating	5 (2 with MMN)	4
2. Large fiber neuropathy	11(4=sensory;7=SM)	7 (1=sensory;6=SM)
3. Small fiber	2	4
Neuropathy sx onset (in yrs after onset of primary condition)	11.8 \pm 4 yrs	26.3 \pm 5.6 yrs
Metronidazole exposure	5 patients	1 patient
Improvement in response to immunotherapy (Assessable in 9 CD and 9 UC patients)	Major:38% Moderate: 38% Mild: 13% None:13%	Major: 11% Moderate: 56% Mild: 33% None: 0%

From Gondim et al, 2005

The controversial metronidazole-related PN

Metronidazole has been associated with PN but the frequency appears to be extremely rare considering the vast numbers of patients regularly treated with this medication.

Gondim *et al* performed an extensive literature review and divided patients into three groups: 1) patients with Crohn's treated with metronidazole (N=74 patients; 14 papers), 2) patients with IBD not treated with metronidazole (N=166; 77 with Crohn's, 89 with UC; 32 papers), and 3) patients without IBD treated with metronidazole (N=13 patients; 11 papers). No clear dose effect was observed in Group #1. Group #s 1 & 2 were difficult to distinguish from each other. The minimum dose reported to result in PN in group #3 was 12 grams (Gondim et al, 2005). [A recent case report described an acute painful sensory PN following an even lower minimum dose of 3.6 grams received over three days (Sarma and Kamath, 2005).] The predominantly sensory PN partially or completely resolved following drug discontinuation when not associated with other medical complications. However, if associated with other medical complications, resolution after drug discontinuation was variable or did not occur at all.

One study of Crohn's patients found no clinical or electrodiagnostic features that differentiated between patients under active treatment, patients who were previously treated, or patients who were never treated with metronidazole. Paresthesias and increased threshold for temperature (documented by quantitative sensory testing) were equally frequent (Stahlberg et al, 1991).

VI. Celiac disease (CD)

CD is a multigenetic, T-cell mediated autoimmune disease that results from a loss of tolerance to gluten (the storage protein found in wheat) and similar proteins in barley and rye. CD is linked closely to the human leukocyte antigen alleles DQ2 and DQ8 and is estimated to occur in up to 1% of the general population. Extraintestinal manifestations are increasingly recognized to be the most common manifestation of this disease in the adult population. Neurological manifestations are estimated to occur in 6-10% of patients with CD, with peripheral neuropathy and ataxia being the most frequently described (Chin and Latov, 2005).

Clinical phenotypes that have been described include: 1) a predominantly sensory neuropathy +/- motor involvement; 2) ataxia (of possibly central or peripheral origin); 3) a severe neuropathy (with extrapyramidal or autonomic features, dysarthria or myoclonus) [Cooke and Smith, 1966; Muller et al, 1996]; and 4) a multifocal sensorimotor axonal polyneuropathy (Chin et al, 2003; Chin and Latov, 2005; Tseng et al, 2005). In a recent study of 164 patients referred for autonomic evaluation, 2.4% were found to have CD and idiopathic dysautonomia, manifest by presyncope and postural nausea with abnormalities in sympathetic and parasympathetic nervous system functions (Gibbons and Freeman, 2005). The results of 8 patients with CD and small fiber neuropathy per skin biopsy were recently described. The epidermal nerve fiber (ENF) density was reduced in five patients and low-normal in 3 patients (2 of whom had morphologic changes in axons). The pattern of ENF density abnormalities in 3 patients suggested a non-length dependent process (Brannagan et al, 2005). An acute motor axonal neuropathy was described in a 12-year-old girl with Turner's syndrome and 'potential' celiac disease (i.e. duodenal biopsy showing increased intraepithelial lymphocytes) [Mata et al, 2005].

Some have found testing for CD in patients with chronic PN to be controversial (Rosenberg and Vermeulen, 2005); however, the diagnostic yield may be higher in patients with evidence of a small fiber pattern of neuropathy (Chin et al, 2003; Rosenberg and Vermeulen, 2005) due to an immune-mediated process or sensory ganglionopathy.

The PN may stabilize in response to a gluten-free diet; however, this has never been assessed prospectively and recent data suggest that the presence of PN appears independent of a gluten-free diet (Luostarinen et al, 2004; Briani et al, 2005). An immune-mediated mechanism resulting in persistent inflammation, independent of gluten exposure, is suspected.

VII. Viral hepatitis

A variety of neuropathies have been reported to occur early in the course of acute viral infection (by hepatitis A, B or C), including acute or chronic demyelinating polyneuropathy or mononeuropathy multiplex involving cranial or peripheral limb

nerves. The most clinically important of the viral hepatitis-induced neurologic complications are those related to hepatitis C infection and cryoglobulins, which are immunoglobulins that precipitate at low temperatures. Cryoglobulinemia may be classified by three patterns: type I=monoclonal; type II mixed=monoclonal (IgM) and polyclonal (IgG); type III mixed=polyclonal (IgM and IgG) [Lange and Tolunsky, 2002].

Hepatitis C

Mixed cryoglobulins (MC), particularly type II, have been reported in ~50% of patients with HCV. The three major constituents of HCV-associated MC are IgM rheumatoid factor, polyclonal IgG and HCV RNA. The IgM rheumatoid factor is monoclonal (type II MC) or polyclonal (type III MC) and targets the Fc region of polyclonal IgG directed against HCV. Other biologic abnormalities may include thrombocytopenia, autoantibodies (e.g. anticardiolipin, antithyroglobulin or antismooth muscle cell antibodies), and hypocomplementemia [low serum C4 and CH50 levels] (Monti et al, 1995). The main clinical complication of MC is vasculitis, which is associated with purpura, arthralgias, kidney disease, and PN (Cacoub et al, 2000).

In a prospective study of 321 patients, 50% of whom were cryoglobulin positive, 9% (28/321) had PN (Cacoub et al, 2000). In a study of 26 patients with HCV/mixed cryoglobulinemia, 77% had PN, defined by the presence of paresthesias (Ferri et al, 1992).

HCV-associated neuropathy is typically painful, particularly if associated with vasculitis. An asymmetric, motor and sensory neuropathy may develop, beginning with multiple mononeuropathies mainly involving the lower limbs (Authier et al, 2003). CIDP and also a sensory>motor axonal neuropathy have been described in association with hepatitis C. Cryoglobulin-negative patients may also develop PN. In one study 50% (10/20) of patients with non-cryoglobulinemic HCV had electromyographic evidence of PN. Genotype Ib was the most prevalent subtype (Paoletti et al, 2000). Other described presentations include anterior ischemic optic neuropathy and restless legs syndrome with small fiber neuropathy (Tembl et al, 1999; Nemni et al, 1987).

Interferon (IFN)- α is thought to protect against autoimmunity, but in some cases it may induce autoimmunity possibly through cytokine-induced immune dysregulation. New onset or worsening of neuropathy after treatment with IFN- α has been infrequently reported and does not appear to be dose dependant (Meriglioli and Rowin, 2000; Marzo et al, 1998).

Pathophysiology

HCV RNA has been detected in skin and nerve biopsy samples showing vasculitis, presumably via vascular deposition of HCV RNA-containing MC, direct infection of endothelial or perivascular mononuclear inflammatory cells (Cacoub et al, 2005). In a study of 30 HCV-infected patients presenting with peripheral neuropathy, 10 had positive-strand genomic HCV RNA (9 in muscle; 3 in nerve); however, negative-strand replicative HCV RNA was never detected. These findings suggested that the neuropathy results from virus-triggered immune-mediated mechanisms rather than direct nerve

infection and in-situ replication (Authier et al, 2003). Hepatocellular failure or deposition of immune complexes in nerve might be other pathogenic mechanisms particularly in chronic hepatitis.

Treatment

Treatment of HCV-associated PN has been based on optimal treatment of the virus itself. Currently, the optimal treatment consists of the combination of IFN- α (or peginterferon- α , the long acting form of IFN) and ribavirin for 18-24 months is (Cacoub et al, 2005). Immunomodulatory therapy may also be beneficial in selected cases. Corticosteroids may be helpful initially for minor inflammatory signs but not in cases of major organ involvement such as in vasculitis. Plasma exchange is performed to control life-threatening symptoms of vasculitis. Rituximab has been used in patients with HCV/MC vasculitis resistant to IFN- α , resulting in a complete clinical response in 80% of patients with disappearance/deletion of peripheral B-cell clones. However, HCV RNA levels increased, possibly due to the decline of immunoglobulins with presumably neutralizing properties (Sansonno et al, 2003; Zaja et al, 2003).

VIII. Porphyria

Porphyria designates a group of rare metabolic disorders characterized by enzymatic defects in the biosynthesis of heme, a metalloporphyrin that is the principal product of porphyrin metabolism. The different forms of porphyria are classified on the basis of which tissues they preferentially affect or where the metabolic defect occurs. The acute hepatic porphyrias (which include δ -aminolevulinic acid [ALA] dehydratase deficiency, acute intermittent porphyria [AIP], hereditary coproporphyria, and variegate porphyria) are associated with variable neuropsychiatric manifestations, including neuropathy, which is estimated to develop in 10-40% of patients. The erythropoietic porphyrias (EPP), which are manifest primarily by skin sensitivity, have rarely been associated with PN (Muley et al, 1998).

Porphyric neuropathy occurs in association with other features of an acute attack of hepatic porphyria, such as abdominal pain, altered mental status changes and autonomic dysfunction. Weakness occurs commonly in patients with an acute attack of AIP (Elder et al, 1997; King et al, 2002) or hereditary coproporphyria (Barohn et al, 1994), mimicking Guillain-Barré syndrome with selective vulnerability of motor nerve fibers, particularly the radial and peroneal nerves. Axonal degeneration is usually reported. Subclinical neuropathy (slowed median motor and sensory conduction velocities) has also been described in patients with latent AIP without neurologic deficits at the time of examination (Kochar et al, 2000; Wikberg et al, 2000). The underlying pathophysiology of porphyric neuropathy has not been established, but could be related to disruption of heme protein function or to direct neurotoxicity of elevated porphyrins (Lindberg et al, 1996; Albers and Fink, 2004).

IX. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

MNGIE is an autosomal recessive disorder defined clinically by severe gastrointestinal dysmotility; cachexia; ptosis, ophthalmoparesis, or both; peripheral neuropathy; leukoencephalopathy; and mitochondrial abnormalities, caused by loss-of-function mutations in the thymidine phosphorylase (TP) gene. This results in elevated levels of plasma thymidine and deoxyuridine which lead to subsequent mitochondrial DNA alterations. Electrodiagnostic studies have most often revealed mixed axonal and demyelinating features (Nishino et al, 2000); however, PN with prominent demyelinating features mimicking CIDP has also been described in five patients (Bedlack et al, 2004). (For further details, refer to lecture notes per Dr. Enrica Arnaudo.)

X. Conclusion

Historically, peripheral neuropathy related to GI diseases has been understood in the context of vitamin or nutritional deficiencies caused by socioeconomic deprivation or alcoholism. The advent of gastric surgery (and bariatric surgery in particular) has resulted in an increased understanding of the mechanisms of GI-related neuropathy, nutritional or otherwise. Immune-mediated mechanisms are suspected to play a role in the extraintestinal manifestations of inflammatory bowel disease and celiac disease. Celiac disease, with its known antigen and well-characterized intestinal response, provides a unique opportunity for studying some of these mechanisms. Treatment of neuropathies related to the GI system has typically included nutritional supplementation, treatment of the underlying disease (hepatitis C) or avoidance of precipitating factors (porphyria). The role of immunotherapy remains to be clarified.

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Table 1.0 Vitamin and nutritional derangements and neurologic manifestations

Vitamin/nutrient	Function	Clinical/neurologic manifestation	Diagnosis	RDA	Treatment
B1 (thiamine) deficiency	Cofactor required by four enzymes (including transketolase). Responsible for carbohydrate metabolism	1. Beriberi=severe deficiency Dry=neuropathic Wet=cardiac disease with peripheral edema. 2. Wernicke encephalopathy: ocular changes, ataxia and mental confusion (classic triad) 3. "Burning foot" syndrome Acute/subacute predominantly sensory axonal, length-dependant PN. 4. Optic neuropathy	1. Serum level 2. Erythrocyte transketolase activity 3. TPP effect: measurement of enhancement of enzymatic activity from added thiamine diphosphate (TPP).	1-1.5 mg/day; Body's total store=30-100 mg; stores can be depleted in 6-8 weeks.	50-100 mg/day IV/IM/orally PN may have limited potential for full recovery.
B6 (pyridoxine) deficiency	Cofactor for enzymes involved in amino acid metabolism and synthesis of δ -aminolevulinic acid Role in neuronal excitability?	Deficiency uncommon but increased in pregnancy and by ingestion of estrogens or certain drugs (isoniazid, hydralazine) Skin changes may look like pellagra. Burning feet, painful paresthesias	Urinary xanthurenic acid after tryptophan loading (>50 mg/day is abnormal)	1.8-2.2 mg/day	50-100 mg/day orally
B6 (pyridoxine) excess		Burning paresthesias and ataxia described in patients taking 200-2000 mg/day. Axonal degeneration in sural nerve bx.		NA	D/C leads to improvement but not resolution. Role of gene transfer?
B12 (cobalamin) deficiency	Transmethylation cofactor Source=meat/dairy products	1. Subacute combined degeneration of cord (with pathologic reflexes, distal predominantly large fiber sensory loss, positive Romberg, Lhermitte sign, visual impairment 2. Distal sensory axonal PN may occur in isolation or prior to emergence of spinal cord abnormalities. 3. Demyelinating PN rarely described	1. Serum level (nl=250-1100 pg/ml) 2. Methylmalonic acid, homocysteine=intermediary metabolites. 3. Schilling test to determine cause 4. Intrinsic factor and parietal cell antibodies in pernicious anemia	3-6 μ g/day	1. 1000 μ g IM (multiple regimens): daily for 5 days, then 500-1000 μ g IM every month. 2. 500-1000 μ g daily orally (1% absorbed by passive diffusion).

B2 (Riboflavin) deficiency		Cheilosis, glossitis, keratoconjunctivitis, dermatitis		1.2 mg/day	
Niacin, nicotinic acid deficiency		1. Pellagra: dementia, photosensitive dermatitis, diarrhea (uncommon in developed countries). 2. Less common: encephalopathy, seizures, myoclonus of face/shoulders, cranial neuropathy, cerebellar ataxia, paratonia of limbs or PN.	Clinical determination. Urinary nicotinic acid metabolites	12-20 mg/day	40-250 mg/day orally
C deficiency	Hydroxylation cofactor	Scurvy		45 mg/day	
Folate deficiency	Single carbon transport?	Megaloblastic anemia		200 µg/day	1 mg/day
D deficiency	Calcium transport	Rickets: proximal weakness, bone pain. Myopathic features by EMG.	Serum level	400 IU/day	
E deficiency (α-tocopherol=active form)	Antioxidant, prevents free radical peroxidation and injury to cell membranes. Incorporated into chylomicrons in small intestine. In liver, alpha-tocopherol transfer protein binds and recycles E.	1. Axonal degeneration of peripheral nerve, dorsal root ganglia, posterior columns with resulting symptoms of progressive gait ataxia, loss of vibration/joint position sense, hyporeflexia. Ganglionopathy per EDX studies. 2. Myopathy rare. 3. Abetalipoproteinemia->neuropathy, cerebellar ataxia, ophthalmoplegia, muscle weakness.	1. Serum level: 2. E:total serum lipid ratio	12-15 IU/day	400 mg twice daily.
Copper deficiency		May be induced by excess zinc (used for cold prevention) Myelopathy, sensory ataxia and PN described.		0.5-1.5 mg/day	

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