EDITORIAL

The neurology of enteric disease

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Neurological complications of gastrointestinal, hepatic and pancreatic disease

The gastrointestinal and nervous systems are intimately connected. In this article, we focus on the neurological complications of gastrointestinal, hepatic and pancreatic disease in adult patients.

THE PANCREAS

Pancreatic function is essential for the maintenance of digestive functioning and hormonal balance. The neurological consequences of diabetes are well known and will be discussed in another review in this series. Hypoglycaemia due to insulinoma may present with a changed conscious level, epilepsy, stroke-like episodes, dementia or psychosis, or neuropathy. Shaw and colleagues[1] described a 27-year-old woman with dystonic choreoathetosis. Symptoms and signs may be focal, mimicking structural lesions.

Acute pancreatitis can lead to an encephalopathy, characterised by focal signs, cognitive impairment, seizures and hallucinations.[2] Cerebral imaging is usually normal. Sudden blindness has also been reported secondary to a retinopathy (Purtscher's syndrome)[3] or optic neuritis.[4] Acute pancreatitis may also lead to renal failure and an associated thrombotic microangiopathy characterised by confusion and seizures, and responsiveness to plasma exchange.[5] Gross and coworkers[6] reported four patients with pancreatitis complicated by severe axonal neuropathy. All these patients, however, required intensive care treatment and had been treated with metronidazole. Vallat and Vital[7] reported on a single patient with encephalopathy and axonal neuropathy complicating a severe pancreatitis.

THE GUT

Malabsorption

Malabsorption may occur as a consequence of primary gastrointestinal pathology (eg, coeliac disease) or iatrogenically after extensive resection of the small bowel. Table 1 summarises the neurological consequences of various vitamin deficiencies.

Vitamin B_{12} deficiency may arise due to poor intake (vegans), malabsorption (fish tapeworm, ileal resection, bacterial overgrowth, tropical sprue and post-gastrectomy states), immune-mediated disease (pernicious anaemia) or rarely as a consequence of genetic disorders that affect transporter proteins.[8 9] The neurological complications include a sensory neuropathy, myelopathy, optic nerve dysfunction and altered cognition.[10] It is well recognised that neurological dysfunction can occur without apparent haematological abnormalities (macrocytosis, target cells, etc) or even in the presence of normal levels of vitamin B_{12}.[11] The sensory neuropathy, although axonal, is often upper limb predominant. Subacute combined degeneration of the cord leads to a combination of pyramidal signs, with a marked loss of dorsal column function, which may be irreversible despite early vitamin replacement.

Thiamine deficiency is rare in the developed world, but is still seen in those dependent on alcohol (particularly after intravenous dextrose is given), as a consequence of prolonged vomiting (hyperemesis gravidarum, bulimia), in post-gastrectomy states or in hospitalised patients requiring total parenteral nutrition. The neurological consequences include Wernicke–Korsakoff's syndrome and beri-beri. Wernicke–Korsakoff's syndrome is characterised by opthalmoplegia, ataxia and confusion.[12] These symptoms can occur in isolation, leading to difficulty in diagnosis. Any delay in recognition and treatment may lead to permanent, profound impairment of short-term memory. People dependent on alcohol also seem to be particularly prone to central pontine myelinolysis, induced by rapid changes in serum sodium concentrations. Beri-beri is characterised by a predominantly sensory axonal neuropathy (burning feet) and heart failure.[13]

Niacin deficiency (pellagra) is also rare in the developed world. The classic description includes dementia, dermatitis and diarrhoea. Myoclonus, ataxia and seizures may also occur. Carcinoid syndrome may also lead to pellagra, owing to increased conversion of hydroxytryptophan to serotonin and a consequent deficiency of nicotinamide.[14]

Vitamin E deficiency can arise secondary to malabsorption, cholestatic liver disease, abetalipoproteinaemia, or as a familial (autosomal recessive) condition caused by mutations in the α-tocopherol transfer protein on chromosome 8.[15] Vitamin E deficiency leads to a sensory neuropathy with marked loss of joint position sense and a head tremor. The neurological features can be indistinguishable from Friedreich's ataxia. Large-dose vitamin E supplementation (800 mg/day) may partially reverse the neurological manifestations.

The role of folate deficiency in the development of certain neuropathologies is somewhat controversial, but dementia and neuropathy can result.[16]

Extensive resection of the small bowel can also lead to the development of recurrent encephalopathy, with a metabolic acidosis and raised levels of D-lactate.[17] The combination of bacterial overgrowth, ingestion of carbohydrates and diminished colonic transit resulting in fermentation is thought to lead to D-lactate toxicity and a raised anion gap. Treatment for this is with antibiotics and dietary modification, avoiding carbohydrate-rich foods.

Coeliac disease

Coeliac disease is a prototypic gluten-sensitive disorder.[18] Exposure to gluten-rich foods (wheat, barley or rye) leads to inflammatory changes in the mucosa of the upper small intestine, which usually reverse on a gluten-free diet. Patients still present with features of severe malabsorption (diarrhoea, weight loss and anaemia), but most have relatively minor complaints or regard themselves as asymptomatic. Coeliac disease is picked up because of abnormalities in blood tests, such as anaemia, hypocalcaemia or the discovery of osteoporosis. Coeliac disease is common, with prevalence rates reported as high as 1:82 in the general population.[19] It is strongly associated with HLA DQw2.

A specimen from the upper small intestine for initial biopsy, usually obtained by a fibre optic endoscope, is mandatory for establishing the diagnosis. The histological findings of villous atrophy and crypt hypertrophy, a flat mucosa, from a patient in the Western world almost always indicates coeliac disease, and in practice the diagnosis is accepted on this finding. The advent of reliable serological tests for coeliac disease has greatly aided diagnosis. The detection of anti-endomysial or anti-tissue transglutaminase in the serum is highly predictive (>90%) of the condition.[20] Measurement of tissue transglutaminase is preferred because a large number of tests can easily be carried out and quantitative results generated. Clinicians, however, need to be aware that antibody-negative coeliac disease does occur.[21] Furthermore, these antibodies are measured in the IgA

Table 1 Vitamin deficiencies and neurological disease

	Diseases										
Vitamin	**N**	**O**	**D**	**Cb**	**On**	**Ep**	**Myel**	**Myop**	**Biochemical test***	**Treatment dosage†**	**RDA**
B_1	+	+	+	+	+				Thiamine replacement‡	Severe deficiency 200–300 mg daily	1.4 mg
B_6	+								Serum pyridoxal phosphate§	20–50 mg up to 3× a day	2 mg
B_{12}	+		+	+	+		+		4.5 ml EDTA; 211–911 ng/l	1 mg on alternate days until no further improvement, then 1 mg every 2 months	1 mcg
D								+	5 ml plain tube; winter: 10–50 nmol/l; summer: 15–75 nmol/l	In intestinal malabsorption up to 1 mg (40 000 units daily)	5 mcg
E	+	+		+		+	+	+	5 ml plain tube 11–30 μmol/l	Malabsorption in abetalipoproteinaemia 50–100 mg/kg daily	10 mg
Ni	+		+	+	+	+			Therapeutic response to niacin¶	Given in combination preparations (either oral or intravenous) with other B vitamins, with or without vitamin C	18 mg
R					+				No specific test	Given in combination preparations (either oral or intravenous) with other B vitamins, with or without vitamin C	1.6 mg

Vitamins: B_1, thiamine; B_6, pyridoxine; B_{12}, vitamin B_{12}; D, vitamin D; E, vitamin E; Ni, niacin; R, riboflavin.
Diseases: Cb, cerebellar ataxia; D, dementia; Ep, extrapyramidal disorders; Myel, myelopathy; Myop, myopathy; N, neuropathy; O, ophthalmoplegia; On, optic neuritis.
RDA, recommended daily allowance (taken from NHS Direct website; http://www.nhsdirect.nhs.uk). EDTA, ethylenediaminetetraacetic acid.
*Some biochemical tests are carried out only at special reference laboratories and we would suggest discussion with your local Clinical Chemistry Department. For some trace elements it may be more practical to treat. Vitamin B deficiency often occurs across the board, and so multivitamin replacement is probably most practical.
†Treatment dosages taken from the British National Formulary. 15 March 2006, Joint Publishers: British Medical Association and Royal Pharmaceutical Society of Great Britain.
‡Thiamine replacement may be the most feasible test. Serum thiamine, pyruvate, α-ketoglutarate, lactate, glycoxylate or red cell transketolase activity can be measured. The thiamine loading test is the best indicator of thiamine deficiency.
§Serum pyridoxal phosphate is the primary active metabolite of pyridoxine.
¶Therapeutic response to niacin establishes the diagnosis. Levels of niacin, tryptophan, nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate can be measured and reflect niacin deficiency.
As more and more people consume over the counter vitamins, vitamin toxicity may occur as a perceived therapeutic benefit, accidental consumption or deliberate self-harm.
Acute vitamin A toxicity, headache and drowsiness; chronic vitamin A toxicity, blurred vision and headache; vitamin D toxicity, headache and muscle weakness; vitamin E toxicity, headache and haemorrhagic stroke; thiamine toxicity, stroke; pyridoxine toxicity, progressive sensory ataxia.

fraction of the immune globulins, and so will be absent in case of IgA deficiency, which is 10 times as common in people with coeliac disease. Anti-gliadin antibodies are not pathognomonic for coeliac disease because of low specificity, being reported in more than 10% of normal people.[22]

If coeliac disease is suspected on clinical grounds and a biopsy result confirms the diagnosis, antibody tests are unnecessary. These tests, however, do have a place if the probability of coeliac disease is low, because a negative result will help avoid a biopsy. Antibody tests are useful to screen groups of people at particular risk for coeliac disease but who do not have overt features—for example, relatives of a patient with coeliac disease and patients with type 1 diabetes mellitus—and in monitoring adherence to a gluten-free diet. In addition, a positive test will aid the diagnosis when the biopsy result is equivocal.

Several case reports have highlighted the occurrence of various neurological disorders, including neuropathy,[23] ataxia,[24] dementia,[25] chorea[26] and epilepsy,[27] in patients with established coeliac disease. The mechanism of neuronal damage is unclear and may be immunological or related to trace vitamin deficiency. The response to a gluten-free diet is usually disappointing and no convincing evidence, except a chance association, has yet been published. Patients with established coeliac disease are suggested to be at high risk of developing epilepsy, but a recent study on a large cohort of patients has cast doubts on this assertion.[28] A curious syndrome of occipital calcification (fig 1) and seizures is described in Italian populations with established coeliac disease, but the pathological mechanism is unclear.[29]

Hadjivassiliou and coworkers[30] have proposed that anti-gliadin antibodies are neurotoxic, leading to a variety of neurological syndromes, including ataxia, headache, myopathy, neuropathy and abnormalities in the CNS white matter. This hypothesis has not been universally accepted and remains controversial. Anti-gliadin positivity has been described in various neurological illnesses of established cause (Huntington's disease[31] and spinocerebellar ataxias[32]) and it has been pointed out that other food antibodies (eg, to egg or milk) seem just as prevalent in populations with neurological illness. The "gluten ataxia" hypothesis, if correct, offers the opportunity of treating hitherto inexorable neurological syndromes by simple dietary manipulation, but the evidence presented thus far is not compelling.[33]

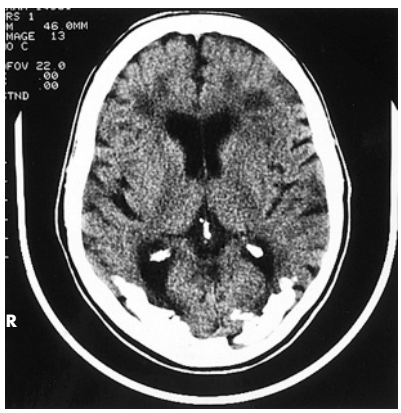

Figure 1 Occipital calcification in coeliac disease.

Whipple's disease

In 1907, Whipple described a rare syndrome characterised by arthralgia, weight loss and steatorrhoea, which was ultimately to bear his name.[34] The causative organism was subsequently identified as *Tropheryma whippelii*, a Gram-positive rod-like actinomycete.[35] In all, 15% of patients have no gastrointestinal symptoms and a few patients have exclusive neurological manifestations.[36] The neurological sequelae are protean and include dementia, myoclonus, epilepsy, hypothalamic dysfunction, ataxia and abnormal eye movements. Oculomasticatory myorrhythmia, although rare, is pathognomonic and is characterised by pendular

oscillations of the eyes synchronised at 1 Hz with involuntary contractions of the masticatory muscles. Uldry and coworkers[37] described a patient with a parkinsonian syndrome who responded to antibiotics, and postulated that *T whippelii* was causal. Involvement of the peripheral nervous system is unusual. Diagnosis can be challenging, but material staining positive to periodic acid Schiff may be found in the CSF or in the small bowel. A polymerase chain reaction-based assay against the causative organism is said to have transformed the ease of diagnosis (although not in our experience).[36] Neuroimaging findings have been reported, ranging from normality to atrophy, white matter, or enhancing lesions and hydrocephalus. Treatment is difficult and relapse is relatively common, but prolonged (2-year) courses of antibiotics have been recommended. No consensus opinion exists on which antibiotics to use, but Anderson[36] has advocated parenteral penicillin or streptomycin for 2 weeks followed by oral cotrimoxazole.

Inflammatory bowel disease

Crohn's disease is an idiopathic transmural inflammatory granulomatous intestinal disorder of unknown cause. Increased platelet activation and a disturbance of clotting factors may result in a hypercoagulable state, which presumably accounts for the excess of venous and arterial cerebral thromboses seen in these patients.[38] The presence of circulating immune complexes, associated autoantibodies (anti-neutrophil cytoplasmic antibodies/antiphospholipid antibodies), or prolonged dehydration and immobilisation secondary to active disease may be other contributory factors. Cerebral arterial events tend to occur in large vessels and affect anterior and posterior circulation.[34] Ischaemic optic neuropathies have also been described, implicating the posterior ciliary vessels.[39]

Crohn's disease causes transmural inflammatory changes, and resultant fistula formation may act as a portal of infection (epidural abscess and meningitis).[40] Epilepsy, myelopathy, multiple sclerosis and axonal (predominantly sensory) neuropathies may prove to be other neurological complications.[34] Humbert and coworkers[41] described a 52-year-old man with Crohn's disease, who developed an axonal neuropathy responsive to plasma exchange.[41]

Ulcerative colitis causes inflammatory changes restricted to the intestinal mucosa and affecting the large bowel.[42] Patients with ulcerative colitis particularly affecting the venous sinuses are at an increased risk for stroke.[43] Postmortem examinations have suggested that venous thrombosis of all sites may complicate ulcerative colitis in 39% of cases but only 1% of patients are clinically affected.[34] Large-vessel and lacunar syndromes have been reported.

The prevalence of general autoimmune disorders in people with ulcerative colitis is three times greater than that in the background population.[44] Acute and chronic inflammatory neuropathies seem to occur more commonly than expected, and it is postulated that *Campylobacter jejuni* may be implicated, as this organism may exacerbate pre-existing inflammatory bowel disease. Optic neuritis has been described in patients with ulcerative colitis,[45] and a familial association of inflammatory bowel disease and multiple sclerosis has been reported.[46]

Enteric neoplasia

Adenocarcinomas often metastasise to the brain (especially the posterior fossa) or the spinal cord. Leptomeningeal carcinomatosis also occurs. Turcot's syndrome is an autosomal dominant or recessive condition characterised by the concurrence of primary brain tumours (medulloblastoma and glioma) with multiple colorectal adenomas.[47]

Miscellaneous disorders

It is well known that autonomic neuropathies, either in the context of diabetes mellitus or in association with more esoteric conditions such as Guillain–Barre's syndrome, can have profound effects on gastrointestinal motility.[48] Intestinal pseudo-obstruction may rarely be a sequel to paraneoplastic processes[49] or to rare genetic syndromes such as familial visceral neuropathy[50] and congenital myopathy.[51] Cunningham and coworkers[52] have suggested that gastro-oesophageal reflux may be caused by parasympathetic (vagal) dysfunction. Several other conditions can cause disordered gastrointestinal motility, including myotonic dystrophy (increased incidence of gallstones),[53] Duchenne's muscular dystrophy,[54] Allgrove syndrome and myoneuronal gastrointestinal encephalopathy. Myasthenia gravis may rarely cause faecal and urinary incontinence.[55] Uterosigmoidostomy may be associated with hyperammonaemic encephalopathy.[56]

THE LIVER

Hepatic encephalopathy

The term ''hepatic encephalopathy'' encompasses a spectrum of clinical severity ranging from reversal of sleep rhythm, to confusion and drowsiness, to coma (table 2).

Hepatic encephalopathy may be the result of acute liver failure (eg, paracetamol overdose, ethylene glycol poisoning or viral hepatitis) or chronic liver disease (eg, alcohol or cirrhosis from any cause).[57] Precipitating factors include an increased protein intake, gastrointestinal bleeding, metabolic derangement (particularly induced by diuretics) and taking sedative or hypnotic drugs. If caused by chronic liver disease, examination often discloses jaundice, liver palms, telangiectasia, hepatosplenomegaly, jaundice or ascites. Extrapyramidal features may be prominent, possibly reflecting pallidal involvement (MRI may show pallidal hyperintensities on T1 weighting).[58] Asterixis (liver flap or negative myoclonus) is a useful sign that is demonstrated by asking the patient to hyperextend the wrists with arms outstretched.[59] Trail-making impairment and the inability to copy a 5-point star may be useful markers of severity in a patient. Blood tests may show hypoalbuminaemia and deranged clotting or liver function tests. Ammonia levels are usually raised, but other toxic metabolites are probably responsible for the clinical picture. An electroencephalogram may show characteristic triphasic waves.[60] Treatment entails reversing the precipitating cause, preventing constipation (lactulose), reducing dietary protein intake and avoiding sedatives. A broad-spectrum antibiotic (eg, neomycin) should also be given.

Table 2 Clinical stages of hepatic encephalopathy

Stage	Clinical features
I	Mild confusion, reversal of sleep rhythm
II	Drowsiness, disorientation, incontinence
III	Somnolent but rousable dysarthria
IV	Coma

The management of fulminant hepatic failure can be extremely challenging.[57] Raised intracranial pressure, cerebral oedema and hypoglycaemia may contribute to the neurological deficits. Monitoring of intracranial pressure is mandatory. The patient should be nursed with the head raised 30° above the horizontal. Intracranial pressure should be maintained below 20 mm Hg, if necessary by the judicious use of mannitol (0.5–1.0 g/kg intravenously over 5 min).

Wilson's disease and other disorders of copper metabolism

Wilson's disease is a rare (birth incidence 17/million) autosomal recessive disorder[61] for which various mutations have been described. Presentation may be hepatic, psychiatric or neurological. In case of neurological presentation, cerebellar and extrapyramidal features

predominate (coarse ''wing-beating'' tremor, parkinsonism, chorea, dystonia, dysarthria and risus sardonicus). Pyramidal signs and seizures also occur. Wilson's disease may cause various systemic effects, including haemolytic anaemia, thrombocytopenia, renal tubular acidosis and rickets. MRI may show the ''face of the panda'' sign.[62] Diagnosis of neurological Wilson's disease is relatively easy, as Kayser–Fleischer rings are invariably present (copper deposited on Descemet's membrane, detectable by slit–lamp examination). Kayser–Fleischer rings can be seen in other conditions such as primary biliary cirrhosis.[63] Serum copper levels may be low, normal or high. Caeruloplasmin levels are usually decreased, but this is an acute-phase protein, whose levels can be falsely raised in chronic liver disease. The 24-h urinary copper excretion is increased. In cases where diagnosis is difficult, giving penicillamine increases excretion of urinary copper. Liver biopsy is rarely required. Lifelong treatment is initially with copper chelators (penicillamine, trientine), and zinc is added as maintenance therapy (prevents copper absorption from the gut). The efficacy of treatment can be monitored by measurement of urinary copper excretion or serum (non-caeruloplasmin-bound) copper. Kayser–Fleischer rings should diminish or disappear with time.[64] The neurological complications are not necessarily reversible. Treatment must be combined with a low-copper diet (copper is found in relatively high concentrations in a variety of foodstuffs, including nuts and chocolate). Other disorders of copper metabolism include Menke's kinky hair syndrome[65] (seizures, mental retardation, skeletal abnormalities with low serum levels of copper and caeruloplasmin) and acaeruloplasminaemia (visual failure and ataxia).[66] Non-Wilsonian hepatocerebral degeneration has also been reported in patients with chronic liver disease and is characterised by dementia, dysarthria, ataxia, tremor, chorea and myelopathy.[67] Swayback is a neurodegenerative disorder in ruminants, which is caused by dietary copper deficiency and characterised by myelopathy and ataxia.[68] Schleper and Stuerenburg[69] have described a similar phenotype in a person with associated low copper levels in the serum and CSF.[69] Factors associated with copper deficiency include malnutrition, prolonged parenteral nutrition and excessive zinc consumption.

Miscellaneous liver disorders

Several metabolic disorders can cause neurological disease with liver involvement:

- Hepatomegaly-sphingolipidoses, mucopolysaccharidoses, peroxisomal disorders, disorders of amino and organic acids, Pompe's disease, galactosaemia.
- Cirrhosis–Wilson's disease, Niemann–Pick, Alpers, peroxisomal disorders, mitochondrial cytopathies, galactosaemia.

EATING DISORDERS AND OBESITY

Anorexia

Patchell[70] reported a high prevalence of reversible neurological complications in patients with anorexia nervosa, including muscle weakness (43%), peripheral neuropathies (13%), headaches (6%), seizures (5%), syncope without orthostatic hypotension (4%), diplopia (4%) and movement disorders (2%).[70] Refeeding of a patient with anorexia nervosa with rapid correction of electrolyte imbalance has been reported to cause central pontine myelinolysis.[71] A refeeding syndrome has also been seen in patients with cancer and in those dependent on alcohol. The pathophysiological basis is thought to be a shift from metabolism of fat to carbohydrate, increased insulin secretion and resultant hypophosphataemia from stimulation of cellular uptake of phosphate.[72] Consequent profound hypophosphataemia can lead to seizures, coma and sudden death.

Pica is a compulsive craving to eat, chew or lick non-food items such as chalk, plaster or rust,[73] and can be linked with mineral deficiency, developmental delay or psychological disturbance. It can result in lead poisoning, malnutrition and electrolyte imbalance.

Obesity

Obesity is a risk factor for vascular disease, particularly hypertension and glucose intolerance. Abdominal obesity rather than increased body mass index is felt to be of particular relevance in stroke.[74] Obstructive sleep apnoea is usually seen in overweight patients and is associated with hypertension and stroke.[75] Obesity is also a risk factor for idiopathic intracranial hypertension.[76] As obesity rates soar, the incidence of idiopathic intracranial hypertension is believed to have increased, particularly in the US. Chronic daily headache appears to be associated with obesity. Gastric surgery is carried out for the treatment of morbid obesity, with an estimated incidence of neurological complications in 15% (depending on the procedure) of cases.[77] B_{12} deficiency is well recognised, but does not account for all the complications seen. Wernicke's encephalopathy has been reported soon after surgery, usually occurring after prolonged and protracted vomiting and possibly as a result of abnormality in an enzyme requiring thiamine. Myelopathy can occur much later (9–30 months), often deriving minimal benefit from vitamin supplementation. Peripheral neuropathy is also reported and is thought to be caused by malnutrition.

Overeating is seen in some neurological conditions, such as the Prader–Willi and Kleine–Levine syndromes. Emerging evidence suggests that eating disorders may be linked to disturbances in hypothalamic and frontotemporal circuits (particularly in the right hemisphere).[78]

FOOD SUPPLEMENTS, TOXINS AND DRUGS

Food supplements

Many vitamin and herbal supplements are available without prescription.[79] Gingko biloba and vitamin E can impair coagulation. St John's Wort may interfere with some anticonvulsants. Bitter orange (*Citrus aurantium*) increases the risk for stroke and seizures, and pennyroyal oil (*Hedeoma pulegioides*) has been associated with neuropathy and seizures. Ephedra or exenadrine has been removed from the US market, because of reported cases of stroke and seizures.

Drugs

The two main classes of drugs used to treat obesity act on the gastrointestinal system (orlistat) and brain (sibutramine). Seizures, tremor and a serotonin syndrome may be a complication of toxic ingestion of sibutramine.

The gastrointestinal complications of various drugs commonly used in neurological practice are summarised below (nausea and vomiting are ubiquitous side effects and have not been considered):

1. Constipation: carbamazepine.
2. Diarrhoea: carbamazepine, catechol-*O*-methyltransferase inhibitors, ethosuximide, lamotrigine, levetiracetam, piracetam, tetrabenazine, tiagabine, triptans, vigabatrin.
3. Dyspepsia: valproate.
4. Flatulence: gabapentin, pregabalin.
5. Gastrointestinal bleeding: levodopa.
6. Pancreatitis: gabapentin, valproate.
7. Retroperitoneal fibrosis: ergot dopamine agonists, methysergide.
8. Weight loss: ethosuximide, topiramate.
9. Weight gain: piracetam, pregabalin, valproate, vigabatrin.

Toxins

Arsenic toxicity is rare, particularly in developed countries, but can cause peripheral neuropathy and encephalopathy.[80] Arsenic poisoning is more commonly found in countries such as Bangladesh, because of contamination of water or the use of traditional remedies. Mercury poisoning related to dental amalgams and contaminated fish is a concern. In the Faeroe Islands, the consumption of contaminated whale meat was believed to be the cause of subtle neuropsychological changes in children.[81] Erethism is the term used to describe an insidious onset of shy, withdrawn behaviour, which, coupled with tremors and gingivitis, can be associated with toxicity due to inhaled (elemental) mercury.[82] Ingestion of contaminated fish containing organic (methyl) mercury is rare and is usually due to industrial accidents. The neurological complications include tremor, ataxia, hearing impairments and visual field constriction. Although mercury-chelating agents are available, they have not proved to be of therapeutic benefit. Lead poisoning is also rare but can occur from drinking contaminated drinking water (lead pipes) or in children who have eaten paint flakes or chips. Cognitive impairment, encephalopathy and peripheral neuropathy can occur.[83] Chelation therapy may be beneficial.

Lathyrism occurs as a result of ingestion of legumes (grass pea) of the genus *Lathyrus*, causing acute spastic paraparesis.[84] The neurotoxic compound is β-*N*-oxalylamino-L-alanine. This condition is endemic in areas such as northwestern Ethiopia and there is no satisfactory treatment for it. Konzo is characterised by a subacute spastic tetraparesis and optic neuritis. It is caused by ingestion of insufficiently processed cassava roots in addition to a low protein intake.[85] Various other tropical syndromes characterised by neuropathy, optic neuritis and myelopathy have been described, including tropical ataxic neuropathy and Strachan's syndrome.[86] The neurological consequences of the ingestion of various seeds, plants and fruits have been reviewed by Carod–Artal.[87]

Botulism is a toxin-mediated disorder of the neuromuscular junction. Although recent reports have suggested an increased incidence of wound botulism[88] among intravenous drug users, infantile botulism from ingestion of contaminated food is still the most common form in the US. Classic botulism occurs within 12–36 h of consumption of contaminated food and consists of dysphagia, ophthalmoplegia and ptosis, followed by weakness in the limbs and respiratory muscles.[89] Treatment with botulinum antitoxin is beneficial, especially if given early.

SUMMARY

The role of liver failure in the development of various neuropathologies is well established. With regard to gluten-sensitive enteropathy, inflammatory bowel and pancreatic disease, most published evidence suggesting that these conditions are associated with neurological complications is at the level of case reportage rather than well-conducted epidemiological surveys. Coeliac disease seems to be associated with a unique syndrome in Italian populations and is characterised by occipital calcification and seizures. The role of gluten as a potential neurotoxin is disputed. Whipple's disease and Wilson's disease, although exceedingly rare, are both potentially treatable but still far more likely to be discussed in grand rounds than seen in real life!

USEFUL WEBSITES

- Coeliac disease: http://www.coeliac.co.uk/
- Dietary advice (NHS Direct): http://www.nhsdirect.nhs.uk/en.asp?TopicID = 656&AreaID = 4316&LinkID = 3391
- OMNI (evaluated online resources): http://omni.ac.uk/browse/mesh/D004066.html

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