

# Gut

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## Leading article

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### Neurological complications of enteric disease

Neurological complications can arise as complications in up to 10% of patients with chronic enteric diseases. The underlying mechanisms may in time offer insights into the pathogenesis of gastrointestinal diseases. This article reviews the complications of adult enteric disease and summarises current theories of pathogenesis.

#### Crohn's disease

Crohn's disease (CD) is an idiopathic intestinal disorder of unknown cause.<sup>1</sup> In contrast with ulcerative colitis, inflammatory changes occur transmurally. Fistula formation may act as a portal of infection. Hefter and coworkers have reported the case of an 18 year old man with CD complicated by a dorsal spinal epidural abscess and meningitis.<sup>2</sup>

Increased platelet activation, leading to multifocal micro infarction in mesenteric vasculature, is the primary event in the pathogenesis of CD.<sup>3</sup> This and disorders of factor V, VIII, fibrinogen, and decreased antithrombin III levels result in a hypercoagulable state, which may be responsible for thromboembolic episodes leading to various neurological deficits.<sup>4</sup> Alternative explanations include the presence of circulating immune complexes<sup>5</sup> as a consequence of vasculitis,<sup>6</sup> associated autoantibodies including antineutrophil cytoplasmic (ANCA) and antiphospholipid antibodies<sup>7, 8</sup> or prolonged dehydration and immobilisation secondary to active disease.<sup>9</sup> Cerebral venous and arterial events have been described. Cerebral arterial occlusions tend to occur in larger vessels including the internal carotid,<sup>10</sup> retinal,<sup>11</sup> and middle cerebral arteries<sup>12</sup> as well as affecting branches of the posterior cerebral circulation.<sup>13</sup> Most patients have active CD at the time of presentation. Cortical venous and sagittal sinus thromboses also occur and may lead to haemorrhagic infarction.<sup>11</sup> Ischaemic optic neuropathy has been described in CD implicating involvement of the posterior ciliary arteries.<sup>14</sup> The reported association of epilepsy and CD may be a reflection of underlying cerebrovascular disease.<sup>15</sup>

Myelopathy has been described in CD<sup>4</sup> and rarely in association with ulcerative colitis (UC).<sup>16</sup> Intriguingly, Minuk and coworkers reported a familial association of multiple sclerosis and CD.<sup>17</sup> However, other studies have shown a similar association between multiple sclerosis and UC.<sup>18, 19</sup> Whether these associations represent shared genetic (HLA) or environmental risk factors is unclear.

Neuropathy has also been reported in association with CD although it occurs more commonly in UC. Whether this is a chance association or reflects a common

aetiological factor (such as an underlying vasculitis) is unclear. Humbert and coworkers described a 52 year old man with CD complicated by a mixed sensori-motor axonal neuropathy, responsive to plasma exchange.<sup>20</sup> Predominantly sensory neuropathies also occur and may predate the clinical manifestations of CD.<sup>21, 22</sup> Folate deficiency has been proposed as an aetiological factor in some cases. In a study of 33 patients with CD, Lindgren and coworkers demonstrated that 48% had sub-clinical involvement of the autonomic nervous system.<sup>23</sup> Other reported peripheral nervous system complications of CD include granulomatous myositis<sup>24</sup> and myasthenia gravis.<sup>25</sup>

#### Ulcerative colitis

In UC, inflammatory changes are confined to the mucosa of the large bowel and granuloma formation is rare. Cerebrovascular disorders have been reported as a complication of UC. Similar aetiological factors to those already described in CD may be responsible for the increased incidence of stroke. Cerebral venous thrombosis is the most commonly reported association.<sup>11, 26</sup> Post-mortem studies have suggested that venous thrombosis of all sites may complicate UC in 39% of cases, but the prevalence in clinical studies is of the order of 1–2% of patients affected.<sup>27</sup> Cerebral large vessel arterial events have also been described, involving anterior<sup>11</sup> and posterior circulations.<sup>28</sup> Lacunar syndromes are also seen.<sup>29</sup> The mean age at presentation is 26 and the underlying colitis is usually active.<sup>28</sup> Cerebral vasculitis<sup>30</sup> and sensori-neural deafness,<sup>31</sup> responsive to immunosuppressant treatment, has also been reported in UC. The prevalence of general autoimmune disorders is three times greater than expected in subjects with UC but not CD.<sup>32</sup>

Various neuropathies have been reported in association with active and quiescent UC. The commonest are acute inflammatory and chronic inflammatory demyelinating polyneuropathies.<sup>4</sup> Acute inflammatory demyelinating polyneuropathies may be precipitated by infection with *Campylobacter jejuni*, which is also associated with exacerbations of inflammatory bowel disease.<sup>33</sup> Immune mediated mechanisms may underlie the enteric and neuropathic manifestations of UC.<sup>34</sup> Sedwick and coworkers described four cases of corticosteroid responsive optic neuritis complicating UC and postulated an autoimmune mechanism.<sup>35</sup> Interstitial myositis has also been reported in association with UC.<sup>36</sup>

### Whipple's disease

In 1907, G H Whipple characterised an illness, mainly of middle aged white men.<sup>37</sup> He described a clinical tetrad of weight loss, diarrhoea, arthralgia, and abdominal pain. In 1949, Black-Schaffer demonstrated periodic acid-Schiff (PAS) staining macrophages within the intestinal mucosa of affected patients.<sup>38</sup> This PAS positive material was shown to be due to the presence of a rod shaped bacteria (*Tropheryma Whippelii*), which has not yet been cultured.<sup>39</sup> PAS positive material has also been demonstrated in the central nervous system<sup>40</sup> and CSF occasionally without concomitant enteric involvement.<sup>41</sup> Postmortem studies have indicated that the nervous system is involved in nearly all cases but clinical manifestations occur in only 10% of patients.<sup>42</sup> The pathogenic mechanisms underlying this disease remains obscure but may be related to defective cell mediated immunity or phagocytosis.<sup>43</sup> The neurological manifestations of Whipple's disease are protean and may occur in isolation leading to diagnostic difficulty.<sup>44-45</sup> The CSF may be entirely normal but an increased protein level,<sup>46</sup> positive oligoclonal bands,<sup>47</sup> and a pleocytosis have been described.<sup>45</sup> Computed tomographic brain scanning may also be normal but a variety of changes have been reported, including atrophy,<sup>40</sup> low density cortical lesions with enhancement,<sup>46-48</sup> and isolated hypothalamic enhancement.<sup>44</sup> Magnetic resonance imaging scanning may show white matter lesions on T<sub>2</sub> weighting with gadolinium enhancement.<sup>47-48</sup> The lesions seem to show a particular predilection for the temporal lobes, brain stem, and hypothalamus. A slowly progressive dementia is the commonest clinical neurological complication of Whipple's disease,<sup>49</sup> often in association with signs of brainstem and hypothalamic dysfunction.<sup>40</sup> An unusual movement disorder known as oculomasticatory myorhythmia is specifically associated with Whipple's disease.<sup>49</sup> This is characterised by rhythmic convergence of the eyes and synchronous contraction of the masticatory muscles with an associated vertical gaze palsy.<sup>50</sup> Other CNS features include ataxia,<sup>45</sup> seizures,<sup>46</sup> myoclonus,<sup>51</sup> and pyramidal weakness as a consequence of multiple intracerebral mass lesions leading to raised intracranial pressure.<sup>47</sup> Uldry and coworkers described a patient with a parkinsonian syndrome responding to treatment with antibiotics.<sup>52</sup> A neuropathy of demyelinating type has also been reported<sup>40</sup> but this could have been a coincidental finding as PAS positive macrophages have not been identified in peripheral nerves.<sup>53</sup> Swash and coworkers described a myopathy in association with Whipple's disease where PAS positive macrophages were seen on multiple biopsy.<sup>54</sup>

In the pre-antibiotic era Whipple's disease was uniformly fatal. Antibiotics that display good CNS penetration (such as chloramphenicol and co-trimoxazole) in combination with penicillin and tetracycline may lead to considerable clinical improvement.<sup>47</sup> However prolonged courses are often needed and CNS relapse is common.<sup>55</sup>

### Coeliac disease

Coeliac disease (gluten sensitive enteropathy) is an autoimmune disorder characterised by malabsorption, steatorrhoea, and weight loss associated with characteristic lesions of the small bowel mucosa, which improve after withdrawal of gluten from the diet. It is often associated with the presence of various serological markers including anti-endomysial and anti-gliadin antibodies. Neurological complications arise in 10% of patients.<sup>56</sup>

Epilepsy occurs in 5% of adults with coeliac disease.<sup>57</sup> Chapman and coworkers surveyed 185 patients with coeliac disease and reported nine (5.5%) with epilepsy of which seven had complex partial seizures.<sup>58</sup> This finding

remains unexplained but intriguingly, seizure control improved in three patients after the introduction of a gluten free diet. The contribution of hypocalcaemia and magnesium deficiency in the development of seizures is unclear. The combination of coeliac disease, epilepsy, and occipital calcification has also been described.<sup>57</sup> Seizures tend to be of partial type and may be associated with underlying folate deficiency. In many patients the underlying coeliac disease is asymptomatic. A subset of these patients may develop drug resistant seizures with concomitant intellectual decline.<sup>59</sup> Cerebellar ataxias may also complicate coeliac disease. These syndromes tend to be progressive, respond poorly to treatment with a gluten free diet, and are associated with minimal or no enteric symptoms.<sup>60</sup> Ward and coworkers described a 47 year old man with a progressive cerebellar ataxia and normal vitamin E concentrations.<sup>61</sup> The institution of a gluten free diet led to a resolution of his abdominal but not his neurological symptoms. A 57 year old man who presented with a pan-cerebellar syndrome, internuclear ophthalmoplegia and palatal myoclonus has also been reported.<sup>56</sup> The neurological complications were progressive despite a gluten free diet. Histological analysis of the brainstem and cerebellum at postmortem examination showed profound Purkinje and dentate cell loss. Lu and coworkers described two patients who presented with progressive cerebellar ataxia, myoclonus, and epilepsy (Ramsay-Hunt syndrome).<sup>62</sup> Both had mild folate and vitamin E deficiency but failed to improve with vitamin replacement.

Other immunological disorders such as diabetes mellitus are associated with coeliac disease and do not improve with a gluten free diet.<sup>63</sup> They may arise as a consequence of circulating immune complexes or the passage of antigens across the damaged small bowel mucosa. A 39 year old woman with coeliac disease, bilateral papillitis, and positive anti-neutrophil cytoplasmic antibodies (ANCA) has also been described.<sup>64</sup> Collin and coworkers reported a series of five patients with coeliac disease and dementia presenting between the ages of 30 and 64.<sup>65</sup> The classic features of coeliac disease were either minimal or absent. All the patients had severe cerebral atrophy shown with computed tomography. Circulating immune complexes were found in four of five patients. A multifocal progressive neurological disorder characterised by ataxia, dementia, epilepsy, myoclonus, and posterior column demyelination is also seen.<sup>66</sup> Patients are usually male and progression is relentless despite gluten free diet. In these cases gastrointestinal symptoms usually precede the neurological deficits. Whether this syndrome results from gluten induced toxicity or immunological compromise is unclear. Kepes and coworkers have reported the occurrence of progressive multifocal leucoencephalopathy with prolonged survival developing in a patient with coeliac disease.<sup>67</sup> They postulated that mild, temporary immunodeficiency could account for the protracted disease course. Unfortunately, the diagnosis of coeliac disease was not established by small bowel biopsy and concentrations of the various immunoglobulin subclasses (such as IgA) were not measured.

Peripheral neuropathies have been described in association with coeliac disease and may be of axonal or demyelinating type.<sup>68</sup> Men are more often affected and gastrointestinal symptoms precede the development of neuropathy. The neurological symptoms often respond to gluten restriction.

### Malabsorption

Malabsorption results from various abnormalities of small bowel function and may complicate diverse illnesses



## Heading missing

	N	O	D/E	CA	RN	ExP	MYEL	MYOP
B <sub>1</sub>	+	+	+	+	+	-	-	-
B <sub>6</sub>	+	-	-	-	-	-	-	-
B <sub>12</sub>	+	-	+	+	+	-	+	-
D	-	-	-	-	-	-	-	+
E	+	+	-	+	-	+	+	+
N	+	-	+	+	+	+	-	-
R	-	-	-	-	+	-	-	-

B<sub>1</sub>=Thiamine, B<sub>6</sub>=pyridoxine, B<sub>12</sub>=vitamin B<sub>12</sub>, D=vitamin D, E=vitamin E, N=niacin, R=riboflavin. N=neuropathy, O=ophthalmoplegia, D/E=dementia/encephalopathy, CA=cerebellar ataxia, RN=retinobulbar neuritis/amblyopia, ExP=extrapyramidal disorders, MYEL=myelopathy, MYOP=myopathy. +=association, -=no association.

including coeliac disease, CD, Whipple's disease, tropical sprue, intestinal diverticulosis, and lymphangiectasia and post-gastrectomy states. The precise details of the neurological complications of malabsorption are beyond the scope of this article. However, the neurological manifestations of the resultant vitamin deficiencies are summarised in the Table. The role of folic acid deficiency in the development of neurological complications (such as neuropathy) is controversial<sup>69</sup> and has therefore been excluded. Hypovitaminosis vitamin A has been established as a cause of xerophthalmia and night blindness although it is not usually attended by signs of neurological disease.

## Conclusions

The association of neurological disorders with enteric diseases is well established. UC and CD are complicated by an increased frequency of arterial and venous cerebrovascular disease as a consequence of probable hypercoagulability. In addition, UC is associated with peripheral neuropathy whereas CD has a predilection for causing myelopathy. Whipple's disease may present with isolated manifestations leading to diagnostic difficulty. A variety of brainstem, hypothalamic, and cognitive abnormalities may occur, perhaps mediated by deficiencies of cell mediated immunity. Coeliac disease is strongly associated with epilepsy (especially of partial type), which often responds to gluten restriction. However, various other progressive neurological syndromes occur, often refractory to treatment, which may have an immunological basis.

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