European Journal of Neurology 2007, **14:** 483–492 doi:10.1111/j.1468-1331.2007.01718.x

REVIEW ARTICLE

Neurologic manifestations of ulcerative colitis

R. Scheid[a,b] and N. Teich[c]

[a]*Day Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany;* [b]*Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; and* [c]*Department of Gastroenterology, University of Leipzig, Leipzig, Germany*

Keywords:
autoimmunity, demyelination, inflammatory bowel disease, neurologic disorders, thromboembolism, ulcerative colitis, vasculitis

Received 27 November 2006
Accepted 12 December 2006

Ulcerative colitis (UC) has traditionally been considered to be an inflammatory disease limited to the colonic mucosa. However, since it has been shown that UC is frequently accompanied by various extraintestinal disorders, there is increasing evidence that UC may also manifest in the nervous system. The following review focuses particularly on these possible manifestations of UC, both in the peripheral (PNS), and in the central nervous system (CNS). A systematic literature search according to the MEDLINE database was performed for this purpose. Although a reliable differentiation may clinically not always be possible, three major pathogenic entities can be differentiated: (i) cerebrovascular disease as a consequence of thrombosis and thromboembolism; (ii) systemic and cerebral vasculitis; (iii) probably immune mediated neuropathy and cerebral demyelination. With the exception of thromboembolism and sensorineural hearing loss, evidence for a causal relationship relies merely on single case reports or retrospective case series. Considering the CNS-manifestations, similarities between UC-associated disorders of the white matter and acute disseminated encephalomyelitis (ADEM) are obvious. Epileptic seizures, unspecified encephalopathies and confusional states are most likely epiphenomena that have to be regarded symptomatic rather than as own entities. A prospective study on the neurologic aspects of UC would be very welcome.

Introduction

Ulcerative colitis (UC) is a chronic and debilitating disorder that is characterized by an inflammation of the colonic mucosa. Most often diagnosed in patients aged between 15 and 30 years, it may present at any age. In the USA and Western Europe, the incidence (prevalence) is approximately 7 (200)/100 000. Women and men are equally affected. UC takes a relapsing–remitting course; common symptoms are abdominal pain and bloody diarrhea. Considering the pathogenesis, in addition to a genetic predisposition abnormal and excessive responses to dietary triggers, to unidentified infectious agents, and to the physiologic intestinal flora by an inadequately regulated mucosal immune system are currently being hypothesized [1,2].

Ulcerative colitis can affect any part of the colon, but is often restricted to the left side. Rectal involvement is almost always present. In approximately 30% of patients UC extends proximally to the splenic flexure, which is defined as left-sided or distal colitis. Only 15% of patients present with an extensive colitis, i.e. an inflammation extending beyond the splenic flexure. However, subsequent proximal extension eventually occurs in approximately 35% of patients with initial proctitis or left-sided colitis. Medical treatment consists of stepwise oral or topical mesalamine (or its retarded derivative mesalazine), corticosteroids, and immunosuppressants (6-mercaptopurine, azathioprine and cyclosporine). If there is very limited disease activity, probiotics are equally efficacious as mesalamine. In carefully selected patients, leukocyte apheresis or treatment with specific monoclonal antibodies (see below) may be beneficial. Patients with UC probably bear an increased lifetime risk for the development of colorectal cancer. Therefore, proctocolectomy is recommended in any case of intraepithelial neoplasia in an endoscopically non-resectable polyp, or if a high-grade intraepithelial neoplasia is present in flat mucosa [1,2].

Ulcerative colitis can be regarded as a systemic disorder and a recent editorial in *Gastroenterology* states that 'the effects of inflammatory bowel disease (IBD) extend to every corner of the body' [3]. Patients often suffer from fatigue, weight loss and inappetence. At least once in their lifetime more than half of the patients will be affected by one of the various extraintestinal manifestations (Table 1), all of which considerably diminish quality of life, particularly during active phases of the disease.

Ulcerative colitis is frequently discussed together with Crohn's disease (CD) under the heading IBD.

Correspondence: Dr Rainer Scheid, Day Clinic of Cognitive Neurology, University of Leipzig, Liebigstr. 22a, 04103 Leipzig, Germany (tel.: +49 341 9724980; fax: +49 341 9724989; e-mail: scheid@cbs.mpg.de).

© 2007 EFNS

Table 1 Major extraintestinal (non-neurologic) manifestations of ulcerative colitis

Manifestation/localization	Prevalence (%)	References
Joints		
Peripheral arthritis	7–50	[4–10]
Ankylosing spondylitis		
Skin and mucous membranes		
Aphtous stomatitis	2–50	[4–10,15]
Erythema nodosum		
Pyoderma gangrenosum		
Sweet's syndrome		
Liver		
Primary sclerosing cholangitis	4–20	[5–10]
Autoimmune hepatitis		
Eye		
Conjunctivitis	1–10	[5–11]
Iritis/uveitis		
Lung		
Chronic bronchitis	8–21	[3,5–10,12,13]
Bronchiolitis obliterans		
Asthma		
Pulmonary vasculitis		
Bones		
Osteopenia	40–50	[4–10,14]
Osteoporosis		
Blood		
Anemia (vitamin and iron deficiency)	33	[5,10,15,16]
Hemolytic anemia		
Myelodysplastic syndrome		
Thrombosis and thromboembolism	79–87	[4,17–19]

Nevertheless, UC and CD are most likely discrete entities with a different pattern of associated disorders [1,20,21]. The current review focuses essentially on the probable manifestations of UC in the nervous system. In comparison with other extraintestinal manifestations these have only seldom been reported [22–25]. A systematic literature search in the MEDLINE-database was performed for this purpose, using the key words 'nervous system diseases/and inflammatory bowel diseases/'; 'peripheral nervous system diseases/and colitis, ulcerative/'; 'central nervous system diseases/and colitis, ulcerative/'; 'colitis, ulcerative/and brain/'; 'vasculitis/and colitis, ulcerative/'. However, because there is not always sufficient differentiation, many of the cited studies are to IBD in general.

Pathophysiology

Pathophysiologically, disorders of the peripheral- and central nervous system in association with UC can be ascribed to at least six different mechanisms, which may be present in isolation or in combination: (i) malabsorption and nutritional, particularly vitamin deficiencies, (ii) toxic metabolic agents, (iii) infections as a complication of immunosuppression, (iv) side effects of medication or therapy, (v) thromboembolism, (vi) immunological abnormalities. In addition to these – at least theoretically – clearly defined and distinct etiologies, neurologic signs and symptoms may also be due to a so far speculative and not further specified neuronal influence of enteric disease onto the nervous system (and vice versa). Such a hypothesis may be derived from contemporary theories considering the existence of a 'brain–gut axis', and from results of respective functional neuroimaging studies [26,27].

For didactic and classificatory purposes, it is useful to differentiate between extraintestinal complications and extraintestinal manifestations of UC. Up to now, only thromboembolism and pathologic immune mechanisms can be regarded as likely causes of neurologic manifestations of the underlying disease. In the following, only these will be discussed in detail. For a comprehensive review of the potential and more widespread complications of UC and enteric disease in general in the nervous system (items i–iv of the above listing), the reader may be referred to a recent article by Wills *et al.* [25].

Manifestations of UC in the peripheral nervous system

As has already been mentioned above, well-known causes of peripheral neuropathy like vitamin deficiencies and certain medications have to be differentiated from a primary involvement of the PNS in UC. Repeat or prolonged exposure to steroids may cause myopathy, which needs to be differentiated from a predominant involvement of motor large fibers in individual patients [28]. Table 2 provides an overview of the disorders of the PNS that have been reported in association with UC, even if the level of evidence relies partly on single case reports only. A literature review on this issue

Table 2 Disorders of the peripheral nervous system that have been reported as extraintestinal manifestations of ulcerative colitis (UC)

Kind of manifestation/localization	References
Acute and chronic inflammatory demyelinating neuropathies	[20,29–31]
Axonal sensory and sensorimotor neuropathies	[20,29]
Brachial plexopathy	[20]
Melkersson–Rosenthal syndrome	[20]
Autonomic neuropathy	[32,33]
Optic neuritis	[20,34]
Sensorineural hearing loss	[35–40]
Inflammatory myopathy	[22,41,42]

Sufficient epidemiological data are not available in the literature. Peripheral neuropathies are believed to be amongst the most frequent neurologic disorders in UC [29].

reaching until 2005 can be found in a recent article by Gondim *et al*. [29]. For the following two major categories a causal relationship to UC seems most likely.

Demyelinating and axonal neuropathies

To the best of our knowledge, there are virtually no prospective data abut the association of peripheral neuropathies and UC available in the literature. One small study, which has only been published as an abstract included 16 UC-patients. During a relatively short follow-up of 3 years, the authors found no patients with clinical evidence of peripheral neuropathy. One patient had abnormal electrophysiology findings, however, it is not stated if this patient had UC or CD. Seven patients had abnormal findings on cardiovascular tests, compatible with autonomic dysfunction. The specificity of these findings remains unclear, and again there is no information if these were UC- or CD-patients [43]. There are two larger retrospective studies, consisting of case series of nine and 15 UC-patients, respectively [20,29]. In the first study, six of the nine UC-patients had peripheral nerve disorders, in the first line acute inflammatory demyelinating polyradiculoneuropathies [20]. The incidence of peripheral neuropathy in UC is estimated 1.9%. Noteworthy, all IBD-patients with peripheral neuropathies in this study had UC. There is no detailed information about CSF findings, or response to therapy. If CSF findings were recorded in the reports, there usually was an isolated elevated protein level. In the most recent and so far largest case series, demyelinating (CIDP) as well as small-fiber- and large-fiber axonal neuropathies were present amongst UC-patients, without a clear predominance for a specific type [29]. Interestingly, the authors did not find cases of documented autonomic neuropathy amongst their patients. However, the patients had not been systematically screened for this kind of neural involvement, though. Not least because there was evidence for a therapeutic effect of immunomodulatory therapies, both in the patients with the demyelinating- and in the patients with the non-demyelinating phenotypes, the authors conclude that a primary immune-mediated neuropathy as an extra-intestinal manifestation of UC (and IBD in general) is likely [29].

Sensorineural hearing loss

Sensorineural hearing loss probably represents another immunologic manifestation of UC [35–40]. According to prospective studies, the hearing loss in UC is frequently clinically silent [39,40], which may explain the low prevalence amongst the reported neurologic patients. In our summary of UC-patients with a CNS disorder of possible (auto-)immune origin (see below and Table 2) this manifestation is mentioned only once [35]. Thus, sensorineural hearing loss should be noticed in the neurologic community as a possible manifestations of UC, and should be particularly searched for.

Manifestations of UC in the central nervous system

Thromboembolism and cerebrovascular disease

A complete listing of the respective literature is beyond the scope of this review. However, as early as in the 1930s arterial and venous thromboses complicating UC have been reported [44]. Reports of ischemic strokes and cerebral venous/sinus thromboses followed [4,45–50]. The first systematic studies with small patient series have been published in the late 1970s [51,52]. Etiologically, a non-specific hypercoagulable state as well as cerebral vasculitis have been vaguely hypothesized [20,48,51–53]. Meanwhile, it has been shown that UC patients have a three- to fourfold increased risk of thromboembolism (incidence approximately 6.5%) [17,18], which seems to be independent from the association with classic thrombophilic risk factors such as immobilization, surgery, steroid therapy and others. In a postmortem study, the incidence of systemic thromboembolism was even sixfold higher, suggesting that a large proportion of cases remains clinically undiagnosed [54]. The coagulation cascade, as well as fibrinolysis and platelet functions are altered in UC, resulting in a generalized prothrombotic state [19]. However, neither an increased prevalence of known hypercoagulable disorders nor a correlation with disease activity has been unequivocally proven amongst UC patients [17,18].

Although roughly 90% of the vascular complications in UC are restricted to the peripheral, particularly venous circulation [18,55], it is likely that the majority of cerebrovascular events in UC has to be placed into this context [56]. However, there are no larger systematic or prospective studies of this specific aspect of thromboembolism in UC, and reliable epidemiologic data are lacking. Neither is it clear, whether primary venous [24,25] or arterial strokes [50–53] are more frequent. With respect to the latter, large artery infarctions involving the anterior and posterior circulation, as well as lacunar infarcts have been described [50–52,56,57]. Autochthonous thrombosis, arterio-arterial-, and paradoxical embolism are possible pathogeneses. Lately, an association of UC and thrombotic thrombocytopenic purpura with its risk for small and large cerebral artery thrombosis [58] has also been proposed [59,60].

As a result of malabsorption and medication with folate depleting agents, IBD patients are prone for hyperhomocysteinemia [61,62]. Strictly speaking, hyperhomocysteinemia therefore has to be subsumed under the UC-complications' rubric. However, because there is evidence for a causal relation between homocysteine concentration, atherothrombosis, stroke [63,64], and (ischemic) leukoaraiosis [65,66] it is worth mentioning here briefly.

Epilepsy

Whilst an association of epilepsy and UC has been reported in some review articles [24], small case series, and case reports [22,67] this issue is completely neglected in other reviews of extraintestinal and neurologic manifestations of IBD [10,15,23]. A MEDLINE-search using the key words 'epilepsy/and colitis, ulcerative/' results in five hits, all dating from the 1970s [67–71]. However, none of these papers addresses the question of a potential association of UC and epilepsy specifically. Moreover, if there were an association of epilepsy and IBD, it seems to be preferentially with CD, not with UC [21]. Nevertheless, epileptic seizures in UC-patients may occur in relation to structural or metabolic causes [20,48,50–52]. They thus should be regarded secondary to a neurologic complication or manifestation, but not as a neurologic manifestation of UC itself.

Myelopathy

Myelopathy, clinically presenting as slowly progressive symmetric spastic paraparesis in the absence of a spinal sensory level has also, however rarely, been reported in association with UC [20,72,73]. A linkage with human T-lymphotropic type 1-associated myelopathy (HAM) has been proposed, too [74,75]. Interestingly, the syndrome may develop without spinal MRI-abnormalities [20]. As with other CNS-manifestations of UC, an immune mediated inflammatory origin has been suggested, but possible relationships to medication and nutritional deficiencies have also been discussed [15,20]. Moreover, it is quite obvious that a myelopathy or transverse myelitis may develop as part of a more widespread CNS-disorder like multiple sclerosis (MS), or as part of a vasculitis, as is probably the case in the report by Ray *et al*. (see below) [73].

Cerebral vasculitis

Systemic and organ specific [76–79], also cerebral vasculitis [47,53,80–82] has repeatedly been reported in association with UC, but again there are no systematic studies. In addition to thromboembolism (see above), vasculitis may be a further cause of stroke in UC, linking suspected pathologic immune mechanisms to cerebrovascular disease. The increasing awareness for a coexistence of UC and Takayasu's disease in Japanese patients with a HLA-B52, DR2 haplotype is particularly noteworthy [83–85]. A common genetic basis of the disorders has been hypothesized [86], but exceptions have been reported as well [87].

With respect to the pathogenesis of vasculitis in UC, most authors assume immune-mediated mechanisms, possibly via genetic susceptibility and HLA status, T lymphocyte-mediated cytotoxicity, or immune complex deposition [10,16,35,47,73,88–91]. The association of UC with p-ANCA or atypical ANCA [2] may be a further hint to a presumed (auto-)immune etiology. However, UC-associated ANCA usually lack antigenic specificity for proteinase-3 (PR3) or myeloperoxidase (MPO) and do not have the potential for the development of systemic vasculitis [92]. Noteworthy, a p-ANCA- myeloperoxidase positive UC patient with 'ischemic lesions in the white matter of the brain' has recently been reported [79].

Table 3 provides an overview of the clinical and investigative data of the previously published patients with UC and a disorder affecting the brain obtained from the MEDLINE database search that can most likely be attributed to as auto-immune and/or vasculitic in nature [35,47,80,81,88–91,93,94]. In summary, there seems to be a heterogeneous clinical picture with possible multifocal neurologic involvement. The respective neurologic manifestations may occur independent from the activity of the bowel disease and may also antedate its onset [6,20]. Cerebrospinal fluid (CSF) most often reveals an isolated increase in protein. Although non-specific, ESR and CRP are frequently abnormal. MRI, if performed was always abnormal. Of note, nearly half of the reported patients had neurologic signs and symptoms that developed under steroid therapy.

Noteworthy, there are three reports of neuropathologically proven necrotizing angiitis [47,81,88], a finding which is similar to the acute hemorrhagic variant of acute disseminated encephalomyelitis (ADEM) [95,96]. ADEM is thought to result from a transient autoimmune response directed against myelin or other autoantigens, possibly via molecular mimicry [95,96]. Because UC is characterized by defective epithelial barrier functions that may allow the uptake of luminal antigens and a stimulation of pathologic immune and inflammatory reactions [97], similar pathologic mechanism like in ADEM might be triggered in UC.

© 2007 EFNS European Journal of Neurology 14, 483–492

Table 3 Summary of the clinical, laboratory, and imaging findings of the previously reported patients with UC and non-thromboembolic CNS manifestations, according to the MEDLINE database.

Author	Number, sex, and age of patients	Neurologic signs and symptoms	PNS	MRI/CCT brain	MRI spine	CSF	ESR/CRP	Treatment	Clinical course (Neurologic)	Specific features	Suspected mechanism
Glotzer *et al.* (1964) [88]	1, m, 18	Hemiparesis, hemianopia, personality change	n.d.	n.d.	n.d.	Elevated protein	n.d.	Surgery	Recovery	Toxic megacolon; brain biopsy: 'acute hemorrhagic leukoencephalitis'	Autoimmune
Edwards (1977) [89]	1, m, 28	Headache, hemiparesis, aphasia	n.d.	n.d.	n.d.	Normal	23 mm/h n.d.	Steroids	Secondary worsening after initial improvement	Development of neurologic symptoms under steroids; secondary (?) intracranial hemorrhage	Vasculitis
Friol-Verceletto *et al.* (1984) [80]	1, f, 45	Spastic hemiparesis	n.d.	Normal (CT)	n.d.	Elevated protein, pleocytosis, xantochromia	30 mm/h n.d.	n.d.	n.d.	No timely correlation with UC symptoms; 'hemorrhagic meningitis'; abnormal angiography	Autoimmune vasculitis
Nelson *et al.* (1986) [47]	1, m, 19	Seizures, coma	+	Multiple hyperdens SCWM	n.d.	Elevated protein, pleocytosis	n.d.	Steroids, cyclo-phosphamide	Recovery	Development of neurologic symptoms under steroids; brain biopsy: necrotizing vasculitis	Vasculitis
Ray *et al.* (1993) [73]	1, f, 32	Painful paresthesia, sensory ataxia, hyperreflexia, muscular weakness	+	Multiple hyperint SCWM (T2)	Single hyperint upper cervical cord (T2)	Normal	n.d.	Steroids, azathioprine, cyclo-phosphamide, plasma-exchange	Improvement	No timely correlation with UC symptoms; polymyositis; anti-Jo-1 ABs	Vasculitis, viral infection
Kraus *et al.* (1996) [93]	1, m, 58	Spastic tetraparesis, detrusor hyperreflexia, progressive dementia	+	Multiple hyperint DWM (PD)	Multiple hyperint	Elevated protein, pleocytosis	Normal	Steroids, azathioprine	Improvement	No timely correlation with UC symptoms; brain biopsy: T-lymphocytic infiltration of the WM	n.d.
Dejaco *et al.* (1996) [90]	1, m, 26	Headache, hemiparesthesia, hyperreflexia, cognitive dysfunction	n.d.	Multiple hyperint SCWM (T2, FLAIR)	n.d.	Normal	67 mm/h 6.8 mg/dl	Steroids	Recovery	UC diagnosis 8 months after neurologic symptoms	Vasculitis
Masaki *et al.* (1997) [91]	1, f, 19	Dysarthria, numbness (tongue, extremities), seizures	n.d.	Multiple hyperint SCWM (FLAIR)	n.d.	Elevated protein	n.d. 0.3 mg/dl	Steroids	Recovery	Timely correlation with UC- exacerbation; development under steroids	Vasculitis
Carmona *et al.* (2000) [81]	1, m, 47	Nausea, confusion, hemiparesis, aphasia	n.d.	Single hypodens	n.d.	n.d.	n.d.	n.d.	Death	Probable timely correlation with UC-exacerbation; autopsy: necrotizing vasculitis	Vasculitis
Druschky *et al.* (2002) [94]	1, m, 37	Monoparesis, dysarthria, confusion, coma	n.d.	Multiple hyperint PVWM, cerebellum (T2)	Cervical medullar lesion (T1)	Elevated protein	96 mm/h, 9.1 mg/dl	Steroids azathioprine, cyclosporine	Recovery	Timely correlation with UC- exacerabation	n.d.
Nemoto *et al.* (2004) [35]	1, f, 69	Cranial nerve palsies, hyperreflexia	+	Multiple hyperint midbrain, pons, DWM (T2), atrophy	n.d.	Elevated protein	98 mm/h 2.3 mg/dl	Steroids	Relapses, partial remission	UC-diagnosis 14 months after neurologic symptoms; development under streoids	Autoimmune

Table 3 (Continued)

Author	Number, sex, and age of patients	Neurologic signs and symptoms	PNS	MRI/CCT brain	MRI spine	CSF	ESR/CRP	Treatment	Clinical course (Neurologic)	Specific features	Suspected mechanism
Pandian *et al.* (2006) [82]	1, f, 35	Hemiparesis, unsteady gait	n.d.	ACA-infarction (DWI)	n.d.	n.d.	n.d.	n.d.	n.d.	Development under steroids and cyclosporine; abnormal angiograpy	Vasculitis

ACA, anterior cerebral artery; CRP, C-reactive proteine; DWM, deep white matter; ESR, erythrocyte sedimentation rate; f, female; m, male; hyperdens, hyperdensities (CT); hypodens, hypodensities (CT); hyperint, hyperintensities (MRI); n.d., not done or no information available; PNS, involvement of the peripheral nervous system; PVWM, periventricular white matter; SCWM, subcortical white matter; +, yes.

Demyelinating disorders: multiple sclerosis and acute disseminated encephalomyelitis

On this background, MS and ADEM are therefore important considerations in neurologic patients with UC. MS has repeatedly been associated with UC, both in epidemiological studies [4,12,98–101], and from a neuroimaging point of view [102,103]. It has also been suspected that treatment with sulfasalazine might affect the occurrence of MS [104]. However, because the current diagnostic criteria for MS are probably more reliable than those previously applied [105,106], it is possible that not all patients in whom an association between MS and UC was assumed in previous reports were actually suffering from MS, but rather from a MS-like disease.

Acute disseminated encephalomyelitis is such a MS-like disease and there are, as yet, no generally accepted diagnostic criteria [96,107]. A part of the clinical and imaging findings of the patients summarized in Table 3 indeed resemble those of ADEM, but there are also differences. First, in comparison with several of the reported UC patients [90,94], MRI lesions in ADEM tend to be larger and more globular. Second, oral and intravenous steroids are considered therapeutic and protective in ADEM, whereas five patients of Table 3 [35,47,82,89,91] developed the neurologic signs and symptoms whilst being treated with continuous prednisolone therapy. However, with respect to the frequently precipitating pre-demyelinating illness in ADEM (usually an upper respiratory tract infection) [108], UC may be considered as an equivalent and as a chronic variant of a pre-demyelinating state.

Interestingly, animal studies may point to a link between the demyelinatig lesions of the kind of MS or ADEM in UC and the prothrombotic states characteristic of UC. Astrocytosis and extensive perivenular loss of myelin has been described in rhesus monkeys suffering from UC and cerebral venous thrombosis, and it has been speculated that the demyelinating lesions could have been caused by perivenular edema secondary to venous blockage [109]. Moreover, it is interesting that the cerebral lesions in the monkeys were identical with 'confluent leukoencephalosis and perivascular myelosis of the cerebral type', a demyelinating disease of monkeys [110].

Biologic agents in the therapy of UC and the risk for demyelination

Recently, monoclonal antibodies against anti-tumor necrosis factor α (infliximab, etanercept, and others) [111] and against α_4 integrins (natalizumab, MLN02) [112,113] have been introduced in the treatment of IBD.

However, these therapies carry the risk of severe adverse effects. The induction of lymphoma, opportunistic infections or reactivation of latent infections (e.g. tuberculosis), demyelination, and optic neuritis have been reported [114–117]. The advent of progressive multifocal leukoencephalopathy (PML) under the treatment with natalizumab is particularly noteworthy [118,119]. Since several studies have independently demonstrated an increased prevalence of non-neurologic and neurologic autoimmune disorders amongst IBD, and particularly UC-patients [12,16,101], a heightened awareness of such unforeseen potential drug – disease interactions seems mandatory [3]. Some have advocated a brain MRI to look for silent demyelination before initiating therapies of that kind. This may become the standard in practice. With respect to natalizumab, serial measurements of JC viral load have also been proposed [120].

Conclusions

There is evidence that UC can manifest both in the PNS and in the CNS. With the exception of sensorineural hearing loss and thromboembolism, the available literature largely consists of case reports and retrospective case series. Systematic studies are lacking, and there are no reliable data concerning incidence and prevalence. On the whole, it seems that neurologic involvement occurs rather rarely, but it can not be excluded that clinically relevant associations are not always established in medical practice, resulting in under-reportage. With the possible exception of thromboembolism, the neurologic manifestations of UC are most likely primary immune-mediated disorders. Considering the reportage of demyelinating disorders of the brain, similarities to ADEM are particularly noteworthy. A prospective study of the different aspects of the neurologic manifestations of UC and additional work on its pathogenesis are needed – not at least since monoclonal antibodies have been introduced into the anti-IBD pharmacopoeia. This should also include the testing of an alternative hypothesis: that both, the neurologic disorder as well as UC itself could be different manifestations of a single, so far unspecified autoimmune disease or immunologic imbalance.

References

1. Podolsky DK. Inflammatory bowel disease. *The New England Journal of Medicine* 2002; **347:** 417–429.
2. Friedman S, Blumberg RS. Inflammatory bowel disease. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*, 16th edn. New York: McGraw-Hill, 2005: 1776–1789.
3. Loftus EV Jr. Inflammatory bowel disease extending its reach. Editorial. *Gastroenterology* 2005; **129:** 1117–1120.
4. Sloan WP Jr, Bargen JA, Gage RP. Life histories of patients with chronic ulcerative colitis: a review of 2000 cases. *Gastroenterology* 1950: **16:** 25–38.
5. Nugent FW, Rudolph NE. Extracolonic manifestations of ulcerative colitis. *Medical Clinics of North America* 1966; **50:** 529–534.
6. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976; **55:** 401–412.
7. Monsen U, Sorstad J, Hellers G, Johansson C. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. *American Journal of Gastroenterology* 1990; **85:** 711–716.
8. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *American Journal of Gastroenetrology* 2001; **96:** 1116–1122.
9. Rogler G, Schölmerich J. Extraintestinal manifestations of inflammatory bowel disease [German]. *Medizinische Klinik* 2004; **99:** 123–130.
10. Danese S, Semeraro S, Papa A, *et al*. Extraintestinal manifetations in inflammatory bowel disease. *World Journal of Gastroenterology* 2005; **11:** 7227–7236.
11. Mintz R, Feller ER, Bahr RI, Shah SA. Occular manifestations of inflammatory bowel disease. *Inflammatory Bowel Diseases* 2004; **10:** 135–139.
12. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastoenterology* 2005; **129:** 827–836.
13. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. *Inflammatory Bowel Diseases* 2003; **9:** 104–115.
14. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. *Annals of Internal Medicine* 2000; **133:** 795–799.
15. Hoffmann RM, Kruis W. Rare extraintestinal manifestations of inflammatory bowel disease. *Inflammatory Bowel Diseases* 2004; **10:** 140–147.
16. Snook JA, de Silva HJ, Jewell DP. The association of autoimmune disorders with inflammatory bowel disease. *The Quarterly Journal of Medicine* 1989; **72:** 835–840.
17. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thrombosis Haemostasis* 2001; **85:** 430–434.
18. Miehsler W, Reinisch W, Valic E, *et al*. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004; **53:** 542–548.
19. Twig G, Zandmann-Goddard G, Szyper-Kravitz M, Schoenfeld Y. Systemic thromboembolism in inflammatory bowel disease: mechanisms and clinical applications. *Annals of the New York Academy of Sciences* 2005; **1051:** 166–173.
20. Lossos A, Eliakim A, Steiner I. Neurologic aspects of inflammatory bowel disease. *Neurology* 1995; **45:** 416–421.

21. Elsehety A, Bertorini TE. Neurologic and neuropsychiatric complications of Crohn's disease. *The Southern Medical Journal* 1997; **90:** 606–610.
22. Gendelman S, Present D, Janowitz HD. Neurological complications of inflammatory bowel disease. *Gastroenterology* 1982; **82:** 1065.
23. Pfeiffer RF. Neurologic dysfunction in gastrointestinal disease. *Seminars in Neurology* 1996; **16:** 217–226.
24. Skeen MB. Neurologic manifestations of gastrointestinal disease. *Neurological Clinics* 2002; **20:** 195–225.
25. Wills AJ, Penigran Tengah DS, Holmes GK. The neurology of enteric disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 2006, **77:** 805–810.
26. Konturek SJ, Konturek JW, Pawlik T, Brzozowiki T. Brain-gut axis and its role in the control of food intake. *Journal of Physiology and Pharmacology* 2004; **55:** 137–154.
27. Derbyshire SW. A systematic review of neuroimaging data during visceral stimulation. *American Journal of Gastroenterology* 2003; **98:** 12–20.
28. Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. *Pharmacological Reports* 2005; **57:** 23–34.
29. Gondim FA, Brannagan II, Sander HW, *et al*. Peripheral neuropathy in patients with inflammatory bowel disease. *Brain* 2005; **128:** 867–879.
30. Konagaya Y, Konagaya M, Takayanagi T. Chronic polyneuropathy and ulcerative colitis. *Japan Journal of Medicine* 1989; **28:** 72–74.
31. Zimmermann J, Steiner I, Gavish D, Argov Z. Guillan-Barré syndrome: a possible extraintestinal manifestation of ulcerative colitis. *Journal of Clinical Gastroneterology* 1985; **7:** 301–303.
32. Zincone A, Bogliun G, Crespi V, *et al*. Autonomic neuropathy in ulcerative colitis. *Scand J Gastroenterol* 1995; **30:** 399–400.
33. Straub RH, Antoniou E, Zeuner M, Gross V, Scholmerich J, Andus T. Association of autonomic nervous hyperreflexia and systemic inflammation in patients with Crohn's disease and ulcerative colitis. *Journal of Neuroimmunology* 1997; **80:** 149–157.
34. Sedwick LA, Klingele TG, Burde RM, Behrens MM. Optic neuritis in inflammatory bowel disease. *Journal of Clinical Neuroophtalmology* 1984; **4:** 3–6.
35. Nemoto H, Iguchi H, Ichikawa Y, *et al*. Ulcerative colitis presenting as sensorineural deafness, brainstem encephalopathy, and white matter lesions. *Neurologist* 2004; **10:** 165–168.
36. Hollanders D. Sensorineural deafness – a new complication of ulcerative colitis? *Postgraduate Medical Journal* 1986; **62:** 753–755.
37. Mathews J, Rao S, Kumar BN, Phil M. Autoimmune sensorineural hearing loss: is it still a clinical diagnosis? *The Journal of Laryngology and Otology* 2003; **117:** 212–214.
38. Morís G, Milla A, Ribacoba R, González C. Acute deafness as an extraintestinal manifestation of ulcerative colitis. *European Journal of Internal Medicine* 2005; **16:** 440–442.
39. Kumar BN, Smith MSH, Walsh RM, Green JRB. Sensorineural hearing loss in ulcerative colitis. *Clinical Otolaryngology* 2000; **25:** 143–145.
40. Akbayir N, Caliş AB, Alkim C, *et al*. Sensorineural hearing loss in patients with inflammatory bowel disease: a subclinical extraintestinal manifestation. *Digestive Diseases and Sciences* 2005; **50:** 1938–1945.
41. Bhigjee AI, Bill PL, Cosnett JE. Ulcerative colitis and interstitial myositis. *Clinical Neurology and Neurosurgery* 1987; **89:** 261–263.
42. Sowa JM. Overlapping polymyositis and ulcerative colitis: HTLV-1 infection as an alternative explanation. *Journal of Rheumatology* 1991; **18:** 1939.
43. Crespi V, Bogliun G, Marzorati L, *et al*. Inflammatory bowel disease and peripheral neuropathy. *Journal of Neurology* 1994; **241**(Suppl. 1)**:** 63.
44. Bargen JA, Nelson WB. Extensive arterial and venous thrombosis complicating ulcerative colitis. *Archives of Internal Medicine* 1936; **58:** 17–31.
45. Kehoe EL, Newcomer KL. Thromboembolic phenomena in ulcerative colitis. Two case reports. *Archives of Internal Medicine* 1964; **113:** 711–715.
46. Hilton-Jones D, Warlow CP. The causes of stroke in the young. *Journal of Neurology* 1985; **232:** 137–143.
47. Nelson J, Barron MM, Riggs JE, *et al*. Cerebral vasculitis and ulcerative colitis. *Neurology* 1986; **36:** 719–721.
48. Johns DR. Cerebrovascular complications of inflammatory bowel disease. *American Journal of Gastroenterology* 1991; **86:** 367–370.
49. Derdeyn CP, Powers WJ. Isolated cortical venous thrombosis and ulcerative colitis. *AJNR American Journal of Neuroradiology* 1998; **19:** 488–490.
50. Keene DL, Matzinger MA, Jacob PJ, Humphreys P. Cerebral vascular events associated with ulcerative colitis in children. *Pediatric Neurology* 2001; **24:** 238–243.
51. Mayeux R, Fahn S. Strokes and ulcerative colitis. *Neurology* 1978; **28:** 571–574.
52. Schneidermann JH, Sharpe JA, Sutton DM. Cerebral and retinal vascular complications of inflammatory bowel disease. *Annals of Neurology* 1979; **5:** 331–337.
53. Gonzáles JL, Egido JA, Martínez P, Antón R. *Cerebrovascular manifestations of gastrointestinal diseases [Spanish]. Reviews of Neurology* 1995; **23**(Suppl. 1)**:** S91–S94.
54. Graef V, Baggenstoss AH, Sauer WG, Spittell JA. Venous thrombosis occurring in nonspecific ulcerative colitis. *Archives of Internernal Medicine* 1966; **117:** 377–382.
55. Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clinical Proceedings* 1986; **61:** 140–145.
56. Lossos A, Steiner I. Cerebrovascular disease in inflammatory bowel disease. In: Bogousslavsky J, Kaplan L, eds. *Uncommon Causes of Stroke*. Cambridge: Cambridge University Press, 2001: 161–168.
57. Fukuhara T, Tsuchida S, Kinugasa K, Ohmoto T. A case of pontine lacunar infarction with ulcerative colitis. *Clinical Neurology and Neurosurgery* 1993; **95:** 159–162.
58. Scheid R, Hegenbart U, Ballaschke O, von Cramon DY. Major stroke in thrombotic-thrombocytopenic purpura (Moschcowitz-syndrome). *Cerebrovascular Diseases* 2004; **18:** 83–85.
59. Baron BW, Jeon HR, Glunz C, *et al*. First two patients with ulcerative colitis who developed classic thrombotic thrombocytopenic purpura succesfully treated with medical therapy and plasma exchange. *Journal of Clinical Apheresis* 2002; **17:** 204–206.
60. Hisada T, Miyamae Y, Mizuide M, *et al*. Acute thrombocytopenia associated with preexisting ulcerative colitis successfully treated with colectomy. *Internal Medicine* 2006; **45:** 87–91.

61. Cattaneo M, Vecchi M, Zighetti ML, *et al*. High prevalence of hyperhomocysteinemia in patients with inflammatory bowel disease: a pathogenic link with thromboembolic complications? *Thrombosis Haemostasis* 1998: **80:** 542–545.
62. Oldenburg B, van Tuyl BA, van der Griend R, Fijnheer R, van Berge Henegouwen GP. Risk factors for thromboembolic complications in inflammatory bowel disease: the role of hyperhomocysteinaemia. *Digestive Diseases and Sciences* 2005; **50:** 235–240.
63. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *The New England Journal of Medicine* 1998; **338:** 1042–1050.
64. Casas JP, Bautista LE, Smeeth L, Sharma P, Hingorani AD. Homocysteine and stroke: evidence on a causal link from mendelian randomization. *Lancet* 2005; **365:** 224–232.
65. Hassan A, Beverley JH, O'Sullivan MO, *et al*. Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction. *Brain* 2004; **127:** 212–219.
66. Wang A, Mok V, Fan YH, Lam WW, Liang KS, Wong KS. Hyperhomocysteinemia is associated with volumetric white matter change in patients with small vessel disease. *Jounal of Neurology* 2006; **253:** 441–447.
67. Meadway J. Ulcerative colitis, colitic spondylitis and associated apical pulmonary fibrosis. *Proceedings of the Royal Society of Medicine* 1974; **67:** 324–325.
68. Sclare AB, Geraghty BP. Therapeutic abortion: a follow-up study. *Scottish Medical Journal* 1971; **16:** 438–442.
69. Mattsson A. Long-term physical illness in childhood: a challenge to psychosocial adaptation. *Pediatrics* 1972; **50:** 801–811.
70. Holdsworth L, Whitmore K. A study of children with epilepsy attending ordinary schools. I: their seizure patterns, progress and behaviour in school. *Developmental Medicine and Child Neurology* 1974; **16:** 746–758.
71. Hill O. The psychological management of psychosomatic diseases. *British Journal of Psychiatry* 1977; **131:** 113–126.
72. Gibb WRG, Dhillon DP, Zilkha KJ, Cole PJ. Bronchiectasis with ulcerative colitis and myelopathy. *Thorax* 1987; **42:** 155–156.
73. Ray DW, Bridger J, Hawnaur J, *et al*. Transverse myelitis as the presentation of Jo-1 antibody syndrome (myositis and fibrosing alveolitis) in long-standing ulcerative colitis. *British Journal of Rheumatics* 1993; **32:** 1105–1108.
74. Suzuki I, Watanabe N, Suzuki J, Yamaguchi E, Munakata M, Fujita M. A case of bronchiectasis accompanied by ulcerative colitis (UC) and HTLV-1 associated myelopathy (HAM) [Japanese] Japanese. *Journal of Thoracic Diseases* 1994; **32:** 358–363.
75. Takegoshi K, Nakanuma Y, Tsukada K, Okuda K. Human T-lymphotropic virus type 1-associated myelopathy and primary sclerosing cholangitis. *Journal of Clinical Gastroenterology* 1991; **13:** 202–204.
76. Barbado FJ, Vazquez JJ, Gil A, Ortiz Vazquez J. Vasculitis and ulcerative colitis. *Gastroenterology* 1980, **79:** 417–418.
77. Iannone F, Scioscia C, Musio A, Piscitelli D, Lapadula G. Leukocytoclastic vasculitis as onset symptom of ulcerative colitis. *Annals of the Rheumatic Diseases* 2003; **62:** 785–786.
78. Kathiresan S, Kelsey PB, Steere CA, Foster CS, Curvelo MS, Stone JR. Case records of the Massachusetts General Hospital. Case 14–2005: a 38-year-old man with fever and blurred vision. *The New England Journal of Medicine* 2005; **352:** 2003–2012.
79. Panani AD, Grigoriadou M, Magira E, Roussos C, Raptis SA. Perinuclear antineutrophil cytoplasmatic antibody myeloperoxidase-positive vasculitis in association with ulcerative colitis. *Clinical Rheumatology* 2005; **25:** 35–37.
80. Friol-Verceletto M, Mussini JM, Bricout JH, Magne C. Ulcero-hemorrhagic rectocolitis. Possible manifestation, angiitis of the central nervous system [French]. *Presse Medicine* 1984; **13:** 1218.
81. Carmona MA, Jaume Anselmi F, Ramirez Rivera J. Cerebral thrombosis and vasculitis: an uncommon complication of ulcerative colitis. *Boletin – Asociation Medica de Puerto Rico* 2000; **92:** 9–11.
82. Pandian JD, Henderson RD, O'Sullivan JD, Rajah T. Cerebral vasculitis in ulcerative colitis. *Archives of Neurology* 2006; **63:** 780.
83. Achar KN, Al-Nakib B. Takayashu's arteritis and ulcerative colitis. *American Journal of Gastroenterology* 1986; **81:** 1215–1217.
84. Morita Y, Yamamura M, Suwaki K, *et al*. Takayashu's arteritis associated with ulcerative colitis; genetic factors in this association. *Internal Medicine* 1996; **35:** 574–578.
85. Masuda H, Ishii U, Aoki N, *et al*. Ulcerative colitis associated with Takayashu's disease in two patients who received protocolectomy. *Journal of Gastroenterology* 2002; **37:** 297–302.
86. Numano F, Miyata T, Nakajima T. Ulcerative colitis, Takayasu arteritis and HLA. *Internal Medicine* 1996; **35:** 521–522.
87. Hokama A, Kinjo F, Arakaki T, *et al*. Pulseless hematochezia: Takayashu's arteritis associated with ulverative colitis. *Internal Medicine* 2003; **42:** 897–898.
88. Glotzer DJ, Yuan RH, Patterson JF. Ulcerative colitis complicated by toxic megacolon, polyserositis and hemorrhagic leukoencephalitis with recovery. *Annals of Surgery* 1964; **159:** 445–450.
89. Edwards KR. Hemorrhagic complications of cerebral arteritis. *Archives of Neurology* 1977; **34:** 549–552.
90. Dejaco C, Fertl E, Prayer D, *et al*. Symptomatic cerebral microangiopathy preceding initial manifestation of ulcerative colitis. *Digestive Diseases and Sciences* 1996; **41:** 1807–1810.
91. Masaki T, Tetsuichiro M, Shinozaki M, Kuroda T. Unusual cerebral complication associated with ulcerative colitis. *Journal of Gastroenterology* 1997; **32:** 251–254.
92. Bartůňková J, Tesař V, Šedivá A. Diagnostic and pathogenic role of antineutrophil cytoplasmatic autoantibodies. *Clinical Immunology* 2003; **106:** 73–82.
93. Kraus JA, Nahser HC, Berlit P. Lymphocytic encephalomyeloneuritis as a neurologic complication of ulcerative colitis. *Journal of Neurological Sciences* 1996; **141:** 117–119.
94. Druschky A, Heckmann JG, Druschky K, *et al*. Severe neurological complications of ulcerative colitis. *Journal of Clinical Neurosciences* 2002; **9:** 84–86.
95. Garg RK. Acute disseminated encephalomyelitis. *Postgraduate Medical Journal* 2003; **79:** 11–17.
96. Menge T, Hemmer B, Nessler S, *et al*. Acute disseminated encephalomyelitis: an update. *Archives of Neurology* 2005; **62:** 1673–1680.

97. Velin ÅK, Ericson AC, Braaf Y, *et al*. Increased antigen and bacterial uptake in follicle associated epithelium induced by chronic psychological stress in rats. *Gut* 2004; **53:** 494–500.
98. Rang EH, Brooke BN, Hermon-Taylor J. Association of ulcerative colitis with multiple sclerosis. *Lancet* 1982; **2:** 555.
99. Minuk GY, Lewkonia RM. Possible familial association of multiple sclerosis and inflammatory bowel disease. *The New England Journal of Medicine* 1986; **314:** 586.
100. Sadovnick AD, Paty DW, Yannakoulias G. Concurrence of multiple sclerosis and inflammatory bowel disease. *The New England Journal of Medicine* 1989; **321:** 762–763.
101. Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. *Gastroenterology* 2005; **129:** 819–826.
102. Geissler A. Focal white-matter lesions in brain of patients with inflammatory bowel disease. *Lancet* 1995; **345:** 897–898.
103. Hart PE, Gould SR, MacSweeney JE, *et al*. Brain white-matter lesions in inflammatory bowel disease. *Lancet* 1998; **351:** 1158.
104. Gold R, Kappos L, Becker T. Development of multiple sclerosis in patient on long-term sulfasalazine. *Lancet* 1990; **335:** 409–410.
105. Thompson AJ, Montalban X, Barkhof F, *et al*. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. *Annals of Neurology* 2000; **47:** 831–835
106. Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". *Annals of Neurology* 2005; **58:** 840–846.
107. Schwarz S, Mohr A, Knauth M, *et al*. Acute disseminated encephalomyelitis. A follow-up study of 40 adult patients. *Neurology* 2001; **56:** 1313–1318.
108. Dale RC, de Sousa C, Chong WK, *et al*. Acute disseminated encephalomyelitis and multiple sclerosis in children. *Brain* 2000; **123:** 2407–2422.
109. Sheffield WD, Squire RA, Strandberg JD. Cerebral venous thrombosis in the rhesus monkey. *Veterinary Pathology* 1981; **18:** 326–334.
110. Van Bogaert L, Innes JR. Neurologic diseases of apes and monkeys. In: Innes JR, Saunders LZ, eds. *Comparative Neuropathology*. New York: Academic Press, 1962: 67–75.
111. Rutgeerts P, Sanborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *The New England Journal of Medicine* 2005; **353:** 2462–2476.
112. Ghosh S, Goldin E, Gordon FH, *et al*. Natalizumab for active Crohn's disease. *The New England Journal of Medicine* 2003; **348:** 24–32.
113. Feagan BG, Greenberg GR, Wild G, *et al*. Treatment of ulcerative colitis with a humanized antibody to the $\alpha_4\beta_7$integrin. *The New England Journal of Medicine* 2005; **352:** 2499–2507.
114. Mohan N, Edwards ET, Cupps TR, *et al*. Demyelination occurring during anti-tumor necrosis factor alpha for inflammatory arthitides. *Arthritis Rheumatics* 2001; **44:** 2862–2869.
115. Thomas CW Jr, Weinshenker BG, Sandborn WJ. Demyelination during anti-tumor necrosis factor alpha therapy with infliximab for Crohn's disease. *Inflammatory Bowel Diseases* 2004; **10:** 28–31.
116. Mejico L. Infliximab-associated retrobulbar optic neuritis. *Archives of Ophtalmology* 2004; **122:** 793–794.
117. Colombel JF, Loftus EV Jr, Tremaine WJ, *et al*. The safety profile of infiximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. *Gastroenterology* 2004; **126:** 19–31.
118. Van Assche G, Van Ranst M, Sciot R *et al*. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *The New England Journal of Medicine* 2005; **353:** 362–368.
119. Berger JR, Koralnik IJ. Progressive multifocal leukoencephalopathy and natalizumab – unforeseen consequences. *The New England Journal of Medicine* 2005; **353:** 414–416.
120. Ropper AH. Selective treatment of multiple sclerosis. Editorial. *The New England Journal of Medicine* 2006; **354:** 965–967.