Neurologic manifestations of ulcerative colitis

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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.
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’; ‘central nervous system diseases’; ‘colitis, ulcerative’; ‘colitis, ulcerative and brain’; ‘vasculitis’ and colitis, ulcerative’.

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>
<thead>
<tr>
<th>Table 1 Major extraintestinal (non-neurologic) manifestations of ulcerative colitis</th>
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<tbody>
<tr>
<td><strong>Manifestation/localization</strong></td>
</tr>
<tr>
<td>Joints</td>
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<tr>
<td>Peripheral arthritis</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Skin and mucous membranes</td>
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<tr>
<td>Aphthous stomatitis</td>
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<td>Erythema nodosum</td>
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<tr>
<td>Pyoderma gangrenosum</td>
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<td>Sweet’s syndrome</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Primary sclerosing cholangitis</td>
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<td>Autoimmune hepatitis</td>
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<td>Eye</td>
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<tr>
<td>Conjunctivitis</td>
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<tr>
<td>Iritis/uvitis</td>
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<tr>
<td>Lung</td>
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<tr>
<td>Chronic bronchitis</td>
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<td>Bronchiolitis obliterans</td>
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<tr>
<td>Asthma</td>
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<td>Pulmonary vasculitis</td>
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<td>Bones</td>
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<td>Osteopenia</td>
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<td>Osteoporosis</td>
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<tr>
<td>Blood</td>
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<tr>
<td>Anemia (vitamin and iron deficiency)</td>
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<tr>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
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<tr>
<td>Thrombosis and thromboembolism</td>
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</table>

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

<table>
<thead>
<tr>
<th>Kind of manifestation/localization</th>
<th>References</th>
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<tbody>
<tr>
<td>Acute and chronic inflammatory demyelinating neuropathies</td>
<td></td>
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<tr>
<td>Axonal sensory and sensorimotor neuropathies</td>
<td></td>
</tr>
<tr>
<td>Brachial plexopathy</td>
<td></td>
</tr>
<tr>
<td>Melkerson-Rosenthal syndrome</td>
<td></td>
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<tr>
<td>Autonomic neuropathy</td>
<td></td>
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<tr>
<td>Optic neuritis</td>
<td></td>
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<tr>
<td>Sensorineural hearing loss</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myopathy</td>
<td></td>
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</tbody>
</table>

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 about 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 preferentially with CD, not with UC [21]. Neverthe-

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-lymphotrophic 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 partic-

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.
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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number, sex, and age of patients</th>
<th>Neurologic signs and symptoms</th>
<th>PNS MRI/CCT brain</th>
<th>MRI spine</th>
<th>CSF</th>
<th>ESR/CRP</th>
<th>Treatment</th>
<th>Clinical course</th>
<th>Specific features</th>
<th>Suspected mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ray et al. (1993) [73]</td>
<td>1, f, 32</td>
<td>Painful paresthesia, sensory ataxia, hyperreflexia, muscular weakness + Multiple hyperint SCWM (T2)</td>
<td>Single hyperint upper cervical cord (T2)</td>
<td>Normal</td>
<td>n.d.</td>
<td>Steroids, azathioprine, cyclo-phosphamide, plasma-exchange</td>
<td>Improvement</td>
<td>No timely correlation with UC symptoms; polymyositis; anti-Jo-1 ABs</td>
<td>Vasculitis, viral infection</td>
<td></td>
</tr>
<tr>
<td>Kraus et al. (1996) [93]</td>
<td>1, m, 58</td>
<td>Spastic tetraparesis, detrusor hyperreflexia, progressive dementia + Multiple hyperint DWM (PD)</td>
<td>Multiple hyperint</td>
<td>Elevated protein, pleocytosis</td>
<td>Normal</td>
<td>Steroids, azathioprine</td>
<td>Improvement</td>
<td>No timely correlation with UC symptoms; brain biopsy: T-lymphocytic infiltration of the WM</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>Djasco et al. (1996) [90]</td>
<td>1, m, 26</td>
<td>Headache, hemiparesis, hyperreflexia, cognitive dysfunction</td>
<td>Multiple hyperint SCWM (T2, FLAIR)</td>
<td>n.d.</td>
<td>Normal</td>
<td>67 mm/h 6.8 mg/dl</td>
<td>Steroids</td>
<td>Recovery</td>
<td>UC diagnosis 8 months after neurologic symptoms</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Masaki et al. (1997) [91]</td>
<td>1, f, 19</td>
<td>Dysarthria, numbness (tongue, extremities), seizures</td>
<td>Multiple hyperint SCWM (FLAIR)</td>
<td>Elevated protein</td>
<td>n.d. 0.3 mg/dl</td>
<td>Steroids</td>
<td>Recovery</td>
<td>Timely correlation with UC-exacerbation; development under steroids</td>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Dranchiky et al. (2002) [94]</td>
<td>1, m, 37</td>
<td>Monoparesis, dysarthria, confusion, coma</td>
<td>Cervical medullar lesion (T1)</td>
<td>Elevated protein</td>
<td>96 mm/h, 9.1 mg/dl</td>
<td>Steroids, azathioprine, cyclophosphamide</td>
<td>Recovery</td>
<td>Timely correlation with UC-exacerbation</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>Nemoto et al. (2004) [35]</td>
<td>1, f, 69</td>
<td>Cranial nerve palsies, hyperreflexia + Multiple hyperint midbrain, pons, DW (T2), atrophy</td>
<td>Elevated protein</td>
<td>98 mm/h 2.3 mg/dl</td>
<td>Steroids</td>
<td>Relapses, partial remission</td>
<td>UC-diagnosis 14 months after neurologic symptoms; development under steroids</td>
<td>Autoimmune vasculitis</td>
<td>Vasculitis</td>
<td></td>
</tr>
</tbody>
</table>
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 α4 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


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