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Peripheral neuropathy in patients with inflammatory bowel disease

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Summary

Peripheral neuropathy (PN) in inflammatory bowel disease (IBD) patients has been reported as individual cases or small series; however, its clinical and electrodiagnostic features have not been well characterized. We conducted a retrospective review of patients with PN and either Crohn's disease (CD) or ulcerative colitis (UC). Eighteen patients with CD and 15 patients with UC were identified after other PN causes were excluded. Male predominance and mean age of PN presentation in the fifties was seen in both groups. Demyelinating neuropathy (CIDP or MMN) occurred in close to 30% of the patients, in a higher percentage of women, than in the non-demyelinating patients. One-third of CD and UC patients had small-fibre or large-fibre sensory axonal PN, while approximately 40% of the CD and UC patients had large-fibre axonal sensorimotor PN. PN symptoms began earlier in the course of CD than in UC ($P < 0.05$). Patients with large-fibre axonal PN were older than patients with small-fibre sensory axonal PN ($P < 0.05$). Close to 60% of each group received immunotherapy with different agents. Half of those treated with CD and 40% with UC had demyelinating PN. Most of the patients who completed immunotherapy in both groups improved; all the patients with demyelinating neuropathy had either moderate or major improvement. The PN syndromes in IBD patients are diverse. Demyelinating forms may occur at any time, but early in the IBD course, pure sensory neuropathy is more common. Response to immunotherapy may occur in both demyelinating and axonal neuropathies.

Keywords: CIDP; Crohn's disease; inflammatory bowel disease; peripheral neuropathy; ulcerative colitis

Abbreviations: CD = Crohn's disease; CIDP = chronic inflammatory demyelinating polyneuropathy; IBD = inflammatory bowel disease; MAG = myelin associated glycoprotein; MGUS = monoclonal gammopathy of undetermined significance; MMN = multifocal motor neuropathy; PN = peripheral neuropathy; QST = quantitative sensory testing; UC = ulcerative colitis

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Introduction

The term inflammatory bowel disease (IBD) is used to describe a group of chronic, recurrent intestinal disorders of complex pathogenesis, which are represented mainly by Crohn's disease (CD) and ulcerative colitis (UC). The extra-intestinal manifestations of CD and UC are diverse. The exact incidence of neurological complications is unknown, with reports varying from 0.2% to 35.7%; the variation could be due to selection bias or to different disease definitions (Greenstein *et al*., 1976; Rankin *et al*., 1979; Gendelman *et al*., 1982; Lossos *et al*., 1995; Elsehety and Bertorini, 1997).

Peripheral neuropathy (PN) is one of the most frequently reported neurological complications (Lossos *et al*., 1995; Elsehety and Bertorini, 1997). Several different PN phenotypes have been described in IBD patients. Parasthesias and increased threshold for temperature detection (which could be indicative of early PN) are common in patients with CD who have been treated with metronidazole (21–39%), but also in those who have not received this medication (19%) (Stahlberg *et al*., 1991). When known risk factors for neuropathy are excluded, such as B12 deficiency and metronidazole exposure, the association between IBD and peripheral neuropathy has been described only in case reports and small series. In the two largest retrospective series designed to study the neurological complications of IBD, the incidence of peripheral neuropathy varied from 0.9% (Lossos *et al*., 1995) to 3.6% (Elsehety and Bertorini, 1997).

In this study, we present the clinical and electrodiagnostic features of PN in patients with CD and UC seen at our centre,

to determine whether they have characteristic clinical presentations. Part of this study has been reported elsewhere as an abstract (Gondim *et al*., 2004).

Patients and methods

We conducted a computer-guided search using the keywords Crohn's disease, ulcerative colitis and inflammatory bowel disease at the Peripheral Neuropathy Center patient databank, Cornell University. A total of 40 medical charts with these characteristics were found and retrospectively reviewed. Patients with either CD or UC whose PN was clearly secondary to other causes (e.g. diabetes, malignancy) were excluded ($N = 4$). In addition, three other charts were excluded because the patients had forms of colonic involvement other than CD or UC (e.g. collagenous colitis). This study was approved by the Weill Medical College of Cornell University Institutional Review Board.

Demographic data, clinical and neurological examination and laboratory and electrodiagnostic studies were analysed. Possible contributory causes of neuropathy, such as remote drug exposure to metronidazole, treated hypothyroidism or B12 deficiency, were noted. Assessment of contributory versus causative role was established by the evaluation of three factors: (i) neuropathy progression despite control of the risk factor (e.g. treatment of B12 deficiency and hypothyroidism); (ii) presence of a neuropathy phenotype not described with the contributory condition (e.g. prior metronidazole exposure and multifocal motor neuropathy) or (iii) occurrence of the contributory factor after the neuropathy onset. Patients were classified into different clinical phenotypes based on neurological exam, clinical complaints, electrodiagnostic tests and nerve biopsy results. Motor abnormalities were established by manual testing of major muscle groups (including intrinsic hand muscles) and functional assessment (e.g. ability to arise from a seated position without using the arms). Patients classified as sensory PN had solely positive (painful PN or paraesthesias) or positive and negative complaints with and without ataxic features and abnormalities in the nerve conduction studies restricted to large sensory fibres. The diagnosis of small-fibre neuropathy was based on clinical history, physical examination and normal nerve conduction studies, and was supported by skin biopsies. Patients classified as sensorimotor PN had motor and sensory changes by history and exam, characteristic of a length-dependent PN with no evidence of demyelination by nerve biopsy or electrodiagnostic testing.

The presence of demyelination was determined by evaluating all nerve conduction studies and/or nerve biopsies, performed in the centre or at outside medical facilities, according to standard criteria [Ad Hoc Subcommittee of the American Academy of Neurology (AAN) AIDS Task Force, 1991]. Demyelinating neuropathies were identified in five CD and four UC patients. Chronic inflammatory demyelinating polyneuropathy (CIDP) was diagnosed according to the clinical and electrophysiological criteria from the AAN (Ad Hoc Subcommittee of the AAN AIDS Task Force, 1991). Multifocal motor neuropathy (MMN) was diagnosed using the American Association of Electrodiagnostic Medicine criteria (Olney *et al*., 2003).

The response to immunotherapy also was graded retrospectively according to the following criteria: (i) *minor*, whenever limited to subjective sensory improvement (substantiated or not by exam); (ii) *moderate*, if in addition to improvement in sensory or gait complaints there was improvement in gait documented by exam or at least a 1-point improvement in strength in at least one muscle group by the Medical Research Council scale; and (iii) *major*, if a substantial change (functional gain or major increase in motor strength) was present. In addition, in the group of patients with positive sensory complaints (pain or paraesthesias), we also grossly graded the response to pain medications (e.g. tricyclic agents, gabapentin) as good, moderate, mild and no response.

A systematic literature review of case reports and series of patients with PN and IBD (treated or not with metronidazole) was also conducted by performing a Medline search and subsequent review of the references from papers published in English, French, Portuguese, German and Spanish. Studies reporting PN in metronidazole-treated non-IBD patients were also included in the literature review, in order to determine whether metronidazole induced different neuropathy patterns in patients without IBD. Two papers written in Japanese but with detailed abstracts in English were also included in the analysis. Descriptive statistics and *t*-test were used to compare the CD and UC groups. Comparisons were considered to be significant at $P < 0.05$.

Results

Demographic characteristics and relationship to IBD activity

Thirty-three patients with IBD-related PN were identified (18 CD and 15 UC) after cases of PN clearly secondary to other causes (e.g. diabetes, malignancy) were excluded ($N = 4$). In Tables 1, 2 and 3 the findings from CD and UC patients are presented. The age of neuropathy presentation in patients with CD and UC was similar: 51.7 ± 2.6 versus 53.3 ± 3.6 years ($P > 0.05$). However, the patients

Table 1 *Summary of the clinical characteristics of CD and UC patients with peripheral neuropathy*

	Crohn's disease ($N = 18$)	Ulcerative colitis ($N = 15$)
Age (years)*	51.7 ± 2.6	53.3 ± 3.6
Percentage of male	78	73
Onset (years)†	11.8 ± 4	26.3 ± 5.6
Demyelinating patients	5 (2 MMN)	4
Large-fibre neuropathy	11	7
Sensory	4	1
Pain/paraesthesias—feet	4	1
Pain/paraesthesias—hands	1	1
Abnormal reflexes	4	1
Distal weakness	1	0
Abnormal gait	2	0
Sensorimotor	7	6
Pain/paraesthesias—feet	6	5
Pain/paraesthesias—hands	2	1
Fasciculations	1	0
Distal sensory loss	7	5
Small-fibre neuropathy	2	4
Pain/paraesthesias—feet	2	4
Pain/paraesthesias—hands	1	1
Decreased pin sensation	2	4
Abnormal reflexes/weakness	0	0

MMN, multifocal motor neuropathy.
*Age of neuropathy presentation; †interval between IBD and neuropathy onset.

Table 2 *Important demographic, clinical and laboratory work-up in CD patients with PN*

No.	Age*	Sex	Gap†	PN	IBD activity	Therapies‡	Response/best agent§
Demyelinating							
1	49	M	20	CIDP	Q; PC	IVIg; Plasm; Flu; Cyc; PM	Major/IV Cyc
2	27	F	−11¶	MMN	RR; fistula	Pred; Flu; IVIg; Cyc; Me; etanercept/Infl**	Major/IV Cyc
3	47	F	1	CIDP	RR; PI	IVIg; MP; Plasm; etanercept**; PM; Pred**	?; Inc (severe side effects)
4	69	M	>1	MMN	Q	Pred; IVIg; Plasm; azathioprine; etanercept**	Major/IVIg
5	50	M	23	CIDP	RR	Pred; IVIg; azathioprine**	Moderate/IVIg
Non-demyelinating							
6	53	M	8	Ax SM	RR	PM	Good
7	47	M	>14	Ax SM	RR	PM	?
8	67	M	44	Ax SM	RR; PC	Plasm; IVIg; PM	Mild (IVIg)
9	52	M	31	Ax SM	RR	Plasm; PM	Moderate
10	65	F	>1	Ax SM	?	Pred (not for neuropathy)	?
11	59	M	>1	Ax SM	Q; PC	IVIg; PM	Moderate
12	63	M	>1	Ax SM	Q	PM	Good
13	59	M	4	Ax S	Q; PSI	IVIg, PM	Moderate
14	52	M	1	Ax S	RR	PM	Good
15	43	M	4	Ax S	RR; PC††	PM	Good
16	52	M	>1	Ax S	Q	PM	Good
17	32	M	8	SF	Q	PM	Moderate
18	46	F	7	SF	RR	IVIg; PM	None

Ax S, large-fibre axonal sensory PN; Ax M, large-fibre axonal sensorimotor PN; CD, Crohn's disease; CIDP, chronic inflammatory demyelinating polyneuropathy; CRAO, central retinal artery branch occlusion; Cyc, cyclophosphamide; F, female; Flu, fludarabine; IBD, inflammatory bowel disease; Inc, incomplete treatment; Infl, infliximab; IVIg, intravenous immunoglobulin; M, male; Me, methotrexate; MMN, multifocal motor neuropathy; MP, methylprednisolone; PC, partial colectomy; PI, partial ileal resection; Plasm, plasmapheresis; PM, pain management; PN, peripheral neuropathy; Pred, prednisone; PSI, partial small intestine resection; Q, quiescent; RR, remitting/relapsing CD course; SF, small fibre.
*Age at PN presentation; †Interval between neuropathy and CD onset, expressed in years (age at CD presentation—age at neuropathy presentation); ‡Therapies employed for neuropathy treatment (in the order of employment); §Response/best immunomodulatory therapy; if no immunomodulatory therapy, response to pain management; ¶Unclear time interval; patient was diagnosed with ''fungal colitis'' for many years until IBD was finally diagnosed; **Not originally used to target PN; ††Multiple surgeries and resections.

Table 3 *Demographic, clinical and neuropathy work-up in Ulcerative Colitis (UC) patients with peripheral neuropathy*

No.	Age*	Sex	Gap†	PN	IBD activity	Therapies‡	Response/best agent§
Demyelinating							
1	48	M	>1	CIDP	Q	IVIg, PM	Moderate
2	58	F	30	CIDP	Q	IVIg	Major
3	70	M	49	CIDP	Q, PC	IVIg, PM	Moderate
4	24	F	>1	CIDP	Q	IVIg, Pred¶, PM	Moderate
Non-Demyelinating							
5	48	M	>1	Ax SM	?	Pred; IVIg, PM	Moderate (IVIg)
6	72	M	30	Ax SM	Q; PC	PM	Good
7	55	F	34	Ax SM	Q, PSI	IVIg; MP; PM	Mild
8	66	M	>1	Ax SM	RR	IVIg; PM	Moderate
9	39	F	>1	Ax SM	Q	PM	Good
10	67	M	4	Ax SM	Q	Prednisone	? (SE)
11	45	M	19	Ax S	RR, PC	IVIg, Pred¶, Met¶; PM	Mild
12	43	M	13	SF	RR	PM	Moderate
13	44	M	>1	SF	?	PM	?
14	48	M	8	SF	Q	PM	None
15	72	M	>50	SF	Q	IVIg, infliximab	Mild? Inc (IVIg)

Ax S, large-fibre axonal sensory PN; Ax M, large-fibre axonal sensorimotor PN; CIDP, chronic inflammatory demyelinating polyneuropathy; Met, methotrexate; MP, methylprednisolone; PC, partial colectomy; PI, partial ileal resection; PM, pain management; Pred, prednisone; PSI, partial small intestine resection; Q, quiescent; RR, remitting/relapsing CD course; SE, side effects; SF, small fibre; SM, sensorimotor.
*Age at neuropathy presentation; †Interval between neuropathy and UC onset, expressed in years (age at UC presentation—age at neuropathy presentation); ‡Therapies employed for neuropathy treatment; §Response/best immunomodulatory therapy; if no immunomodulatory therapy, response to pain management; ¶Used for the treatment of UC and not for PN.

with large-fibre sensorimotor axonal PN were significantly older than the patients with small-fibre or large-fibre sensory axonal PN, regardless of whether one compares CD and UC patients separately ($P = 0.045$ and $P = 0.035$) or combined ($P = 0.0368$): 57.8 ± 2.7 (combined CD + UC), 57.9 ± 2.8 (CD) and 57.8 ± 5.2 (UC) years versus 48.7 ± 3.1 (combined CD + UC), 47.3 ± 3.8 (CD) and 50.4 ± 5.5 (UC) years. Although no significant difference in the age presentation of the PN was seen between the demyelinating and non-demyelinating patients ($P > 0.05$), patients with demyelinating PN had the widest range of age distribution.

Male predominance was evident in both groups: 78% and 73%, respectively. However, in the demyelinating PN patients, 40% of the CD and 50% of the UC patients were women (versus 15% and 18%, in the non-demyelinating groups, respectively). In the CD demyelinating group, the female predominance was even stronger with the exclusion of two demyelinating PN patients who later developed monoclonal gammopathy of undetermined significance (MGUS): 67%.

Neuropathy symptoms began 11.8 ± 4 years after CD onset and 26.3 ± 5.6 years after UC onset ($P < 0.05$). In five CD and six UC patients, the exact interval duration between IBD and neuropathy onset could not be established (although the PN started at least 1 year after IBD onset). Patients with demyelinating PN had a wider range of interval duration between IBD and neuropathy onset in comparison to non-demyelinating patients, but no significant difference. However, except for one older UC patient with long-term IBD course (exact duration unknown) and recent onset of PN, patients with large-fibre axonal PN had a significant longer interval duration between IBD and neuropathy onset (23.6 ± 5.7 years) in comparison to small-fibre and large-fibre sensory axonal PN patients: 8 ± 2 years ($P = 0.0162$). Patients with CD had a recent quiescent IBD course in 39% of the cases, while 56% had a remitting/relapsing course and in 6% IBD evolution could not be detailed. A third of the CD patients underwent partial colectomy or small bowel resection and one patient developed an anal fistula. Patients with UC had a more quiescent course in 67% of the cases, remitting/relapsing in 20% and in 11% the IBD course could not be detailed. Among the UC patients, 27% underwent partial colectomy or small bowel resection. A clear relationship between neuropathy onset/exacerbation and IBD relapse was present in 33% of the CD and in 40% of the UC patients.

Contributory PN factors were identified in 44% of the CD and 20% of the UC patients. Two CD patients had positive hepatitis C serology (patients 8 and 9) and one UC patient was hepatitis B positive (patient 5). None of them had clinical liver disease or cryoglobulinaemia. One CD patient was diagnosed with an IgM kappa and another with IgG kappa monoclonal gammopathy of undetermined significance long after neuropathy presentation and diagnosis of CD (patients 1 and 4). In these two patients, it was clearly not possible to distinguish a determinant versus contributory role since it is possible that MGUS was not diagnosed, but was present, in the early stages. B12 deficiency was remotely diagnosed in three CD patients (patients 1, 11 and 13) and one UC patient (patient 10). However, PN progressed despite adequate B12 deficiency treatment and normal B12 levels.

Five CD patients had remote use of metronidazole (during variable intervals and CD stages). One patient with UC also had a 4-week course of metronidazole, several years prior to neuropathy onset. No clear relationship between metronidazole exposure and neuropathy onset was detected. In this group of patients, progressive neuropathy symptoms were present after stopping this medication (CD patients 3, 9, 14, 15, 18 and UC patient 11).

Other neurological disorders were present in 67% of the CD and in 53% of the UC patients. In the CD group, they included: small vessel disease ($N = 2$), transient ischaemic attacks, spells of diplopia, strokes and intracerebral haemorrhage, seizures, ocular myositis, Bell's palsy, optic neuritis, tremor and central serous retinopathy ($N = 1$, each). In the UC group, they included: Bell's palsy, migraine and small vessel disease ($N = 2$, each), transient ischaemic attacks, spells of diplopia, strokes, sleep apnea and tremor ($N = 1$, each).

Neuropathy phenotype

Crohn's disease patients

Demyelinating phenotypes. Multifocal motor neuropathy. Two patients met the diagnostic criteria for MMN (CD patients 2 and 4). Unilateral hand numbness and cramps marked the onset of PN in patient 2, while patient 4 presented with leg weakness. They subsequently developed motor, sensory and gait complaints. On exam, both patients had proximal and distal *asymmetric* weakness with minor gait impairment. Patient 4 later developed minor sensory changes on exam and chin numbness. Initial electrodiagnostic studies on patient 2 revealed the presence of conduction blocks in the bilateral ulnar and right median nerves at multiple sites, with normal sensory nerve conduction studies, and left ulnar F-wave minimal latency in the demyelinating range with mild–moderate asymmetric motor leg involvement (mildly prolonged bilateral peroneal distal latencies with decreased evoked amplitudes). Subsequent studies revealed a deterioration with a widespread decline in motor-evoked response amplitudes, prolongation of F-wave minimal latencies in the demyelinating range and secondary axonal changes detected by electromyography; however, sensory studies remained normal. Initial electrodiagnostic studies on patient 4 revealed conduction blocks in the left median (at the elbow) and bilateral median and ulnar (with supraclavicular stimulation) nerves, possible conduction block in the right tibial nerve at the popliteal fossa and demyelinating F-wave minimal latencies in multiple nerves with preserved sensory responses. Both patients had normal CSF protein. Patient 2 had moderately elevated anti-GM1 levels (1 : 1600) and oligoclonal bands in the CSF. Patient 4 had an IgM kappa monoclonal gammopathy of undetermined significance. Nerve biopsies were not performed.

Chronic inflammatory demyelinating polyneuropathy: In the three CD patients who met the AAN criteria for CIDP (patients 1, 3 and 5), the initial PN presentation included foot numbness/gait instability (patient 1), burning in the soles of the feet (patient 3) and felt pain and leg weakness (patient 5). They subsequently developed motor, sensory and gait complaints. On exam, all three patients had proximal greater than distal symmetric weakness, with distal sensory impairment/loss and minor–moderate gait impairment. Patient 3 developed a Romberg sign at the later stages. All three patients met the AAN electrodiagnostic criteria for CIDP. Patient 1 (with IgG kappa monoclonal gammopathy of undetermined significance) had elevated CSF protein, while patient 3 had a normal CSF protein. No patient exhibited elevated antibody titres against gangliosides or myelin associated glycoprotein (MAG). No nerve biopsies were performed in this subgroup.

Non-demyelinating phenotypes. Small-fibre neuropathy: Two CD patients had small-fibre, painful PN (see Table 1). Nerve conduction studies were normal. Skin biopsies revealed a length-dependent small-fibre neuropathy with reduced epidermal nerve fibre density, below the fifth percentile of normal (McArthur *et al*., 1998) in patient 18. Patient 17 had morphological changes, which included axonal swellings, axonal proliferation in the subepidermal region of the skin and excessive branching. Patient 17 had additional autonomic complaints (hyperhydrosis, fatigue), although autonomic evaluation (Valsalva manoeuvre, deep breathing, tilting table and sympathetic skin-response testing) did not disclose any abnormality. Quantitative sensory testing (QST) revealed an increased vibratory threshold and decreased tolerance to pain.

Large-fibre axonal neuropathy: The other 11 CD patients had electrodiagnostic abnormalities consistent with a large-fibre axonal PN. Such electrodiagnostic abnormalities were restricted to sensory large fibres in four CD patients (patients 13 to 16), who only had sensory complaints at PN presentation. No motor or autonomic complaints were reported in this subgroup. No patient had high anti-ganglioside or anti-gliadin titres and no spinal taps were performed. Patient 16 had an increased threshold to cold and decreased tolerance to pain stimulation on QST.

Seven other CD patients had electrodiagnostic involvement of sensory and motor large fibres (patients 6–12). In addition to sensory complaints (affecting arms, legs and, in several instances, faces), all patients subsequently developed complaints of weakness and/or mild gait imbalance. Patient 11 had difficulty initiating a urinary stream. Since autonomic symptoms were mild/equivocal, no patient from this subgroup underwent formal testing. The neurological exam revealed distal length-dependent sensory changes with different degrees of motor involvement (motor strength, ability to arise from a chair without using of arms and gait). Nerve biopsies, performed at outside centres, revealed 'chronic axonopathy' in patient 8 and 'chronic axonopathy' with degenerative clusters and Bungner bands as well as thickening of blood vessels with duplication of the basal lamina in patient 11 (no teased fibre studies were done in either study). No patient had high anti-ganglioside or anti-gliadin titres. Patient 11 had normal CSF chemistry. Patient 9 had an increased threshold to vibration/cold and decreased tolerance to pain stimulation on QST.

Ulcerative colitis patients

Demyelinating phenotypes. Chronic inflammatory demyelinating polyneuropathy: Four UC patients met the electrodiagnostic AAN criteria for CIDP (patients 1–4). Demyelinating changes were less prominent than in the CD demyelinating group. Patients also had less weakness than in the demyelinating CD group. Their initial PN presentation included foot or toe numbness/pain (patients 1, 3 and 4) and pain and paraesthesias in the hands and feet (patient 2). They subsequently developed motor and sensory complaints in the legs and arms. Gait was involved in UC patients 2 and 3. Patients 1 and 2 had significant clinical fatigue, and UC patient 2 also had a dry mouth and urinary incontinence. All four patients followed the 'classic CIDP' phenotype with proximal and distal symmetric weakness and distal sensory impairment/loss. However, UC patient 1 had very mild proximal weakness with more prominent sensory findings, and patient 2 had distal greater than proximal weakness. Patient 3 also had a Romberg sign. Nerve biopsies from patients 1 and 2 revealed segmental demyelination/remyelination. Teased-fibre analysis from patient 2 revealed segmental demyelination and remyelination, with remyelination seen in 55% of the fibres. No patient had high antibody titres against gangliosides or MAG.

Non-demyelinating phenotypes. Small-fibre neuropathy: Four UC patients had small-fibre, painful PN. No patient had autonomic complaints. Nerve conduction studies were normal. Skin biopsies revealed a length-dependent small-fibre neuropathy with reduced epidermal nerve fibre density, below the fifth percentile of normal (McArthur *et al*., 1998) in patient 13. Patient 14 had morphological changes, which included axonal swellings, axonal proliferation in the subepidermal region of the skin and excessive branching. No patient had positive anti-ganglioside or anti-gliadin titres and no lumbar punctures were performed. Quantitative sensory testing revealed an increase in the decreased threshold to heat stimulation in patient 13 and decreased tolerance to pain.

Large-fibre axonal neuropathy: The other seven UC patients had abnormalities in the electrodiagnostic studies consistent with a large-fibre axonal PN. Patient 11 had restricted large-fibre sensory axonal abnormalities in the electrodiagnostic studies. He had burning and ''stinging'' pain in the feet and hands at PN presentation. He complained of difficulty using his hands, but otherwise had no motor or autonomic symptoms. Neurological exam revealed hyporeflex with decreased pin in the V2 distribution and in the distal legs.

The other six UC patients had involvement of sensory and motor large fibres demonstrated by electrodiagnostic studies

(patients 5–10). No patients in this subgroup had autonomic complaints. Patient 5 had normal autonomic testing (sympathetic skin responses and heart rate variability on Valsalva). The neurological exam revealed distal length-dependent sensory changes with different degrees of motor involvement (strength, ability to arise from a chair without using the arms and gait). Overall, the degree of motor involvement was less pronounced than in the CD patients with large-fibre sensorimotor axonal involvement. Patient 5 had a nerve and muscle biopsy in an outside facility (without teased fibre evaluation). No patient had high anti-ganglioside or anti-gliadin titres. Patient 5 had a normal CSF profile. Patient 10 had an increased threshold to vibration/cold on QST.

Neuropathy treatment

As can be seen in Tables 2 and 3, immunomodulatory therapy was given to treat PN in 61% (3% also had additional immunomodulatory therapy for IBD with impact in the PN), including 56% of the CD (1 patient had treatment for IBD with impact on the PN) and 67% of the UC patients, at some point during the disease course at this centre or by prior neurologists with IVIg, prednisone, fludarabine, cyclophosphamide, azathioprine, etanercept and/or plasmapheresis. Half of the CD and 40% of the UC patients who received immunotherapy for PN had demyelinating PN (CIDP or MMN). One CD and one UC patient could not have the response to immunotherapy assessed because of early side effects, and another with a mild response had to discontinue immunotherapy prematurely due to side effects.

Immunotherapy of PN in the CD patients who could have the response adequately evaluated (completed course), led to major improvement in 38%, moderate in 38%, mild in 13% and no response in 13% (patients with small-fibre neuropathy, treated by an outside neurologist). Immunotherapy of PN in the UC patients who could have the response adequately evaluated (completed course) led to mild improvement in 33%, moderate in 56% and major in 11%. IVIg was the most-employed agent, but response was variable during the disease course. For several CD patients, more aggressive immunosuppressant therapy with cyclophosphamide was employed. In the following sections, we detail further the responses in the demyelinating and non-demyelinating subgroups.

Demyelinating neuropathy

Crohn's disease: In the demyelinating CD subgroup, immunomodulatory therapy led to major improvement in 60% (75% of the patients who could complete treatment) and moderate in 20% (25% in the patients who could complete treatment). Patient 4 discontinued IVIg early in the treatment due to side effects (headache and anxiety; prednisone also caused psychosis), which precluded an accurate analysis.

A detailed list of each agent employed for each patient can be seen in Table 2. For the two patients with MMN, prednisone led to no benefit for patient 4 and mild improvement for patient 2. Both patients responded well to IVIg therapy (at different doses and protocols). However, early relapses and clinical deterioration even with IVIg in patient 2 led to the administration of a protocol of high dose cyclophosphamide without stem-cell rescue (50 mg/kg for 4 days). Patient 4 had improvement with plasmapheresis (but not with azathioprine), which was improved for a short-term period due to clinical deterioration despite IVIg administration. Both patients reported some subjective benefit of PN symptoms with etanercept (administered for the treatment of CD) and patient 2 also reported mild subjective PN symptoms with inflixamab (used by her gastroenterologist for CD treatment). Patient 2 also had mild PN improvement with the administration of a short course of fludarabine.

The two CD patients with CIDP who tolerated immunomodulatory therapy (patients 1 and 5) had at least a moderate response to IVIg. Patient 1 had allergic reactions to IVIg and then had clinical deterioration. A protocol of high dose cyclophosphamide without stem-cell rescue (50 mg/kg for 4 days) was administered, with major improvement. Patient 1 also had a mild PN response to fludarabine. Patient 5 had mild PN improvement with prednisone and the incidental use of azathioprine for CD had no effect on the PN. Patient 1 was also treated with different neuropathic pain medications, with moderate pain improvement. Patient 3 could not tolerate neuropathic pain treatment with amitriptyline because of side effects.

Ulcerative colitis: In the demyelinating UC subgroup, 25% had major and 75% moderate improvement (Table 3). In contrast to the CD patients, demyelinating PN was only treated with IVIg. However, when prednisone was administered for treatment of the UC, Patient 4 reported subjective improvement of PN symptoms. Other than transient headache in patient 2 (not present when a different brand of IVIg was administered), no side effects of IVIg were reported in this group. Additionally, patients 1, 3 and 4 received treatment for neuropathic pain, which included tricyclic antidepressants and gabapentin. Patient 4 reported improvement of neuropathic pain with the administration of IVIg.

Non-demyelinating neuropathy

Crohn's disease: As one can observe in Table 2, in the non-demyelinating CD subgroup, 60% had a moderate response, 20% mild and 20% no response.

Crohn's disease patients 17 and 18 (small-fibre, painful PN) received therapy for neuropathic pain with different non-immunomodulatory agents (antidepressants, gabapentin), with a moderate response. IVIg therapy was administered by a prior neurologist to patient 18, without pain benefit or change by neurological exam.

Crohn's disease patients 13–16 (large-fibre sensory axonal PN) were treated with a variety of common neuropathic pain medications with a good response. Patient 13 was treated with IVIg and had a moderate response with significant improvement of his gait, better pain control with decreased

medication requirements and with additional sensory improvement confirmed by neurological examination.

CD patients 6–12 (large-fibre sensorimotor axonal PN) were treated with a variety of common neuropathic pain medications with mild to good responses (except patient 10 who was only treated with prednisone). Patients 8 and 11 received IVIg and patients 8 and 9 had plasmapheresis. These three patients treated with immunomodulatory therapy had mild–moderate responses (Table 2) with the best response after IVIg administration.

Ulcerative colitis: As can be seen in Table 3, in the non-demyelinating UC subgroup, 51% had mild improvement (60% of the patients who completed immunomodulatory treatment), 34% moderate improvement (40% of the patients who completed immunomodulatory treatment) and side effects precluded the evaluation of the response in 17%.

UC patients 12–15 (small-fibre, painful neuropathy) were treated for neuropathic pain with different agents (antidepressants, gabapentin, Lidoderm). Response could not be assessed in patient 13. No response was observed in patient 14. Patients 12 and 15 had moderate responses. Patient 15 had PN onset after prednisone and azathioprine were tapered off when he was treated for pyoderma gangrenosum and UC relapse. This led to the suspicion of ongoing immune-mediated PN. He initially had infliximab infusions, which were ineffective. A trial of IVIg was started and the neuropathic pain improved, with decreased dose requirements of gabapentin. However, IVIg was subsequently discontinued because of increased creatinine levels.

Ulcerative colitis patient 11 (restricted, sensory, axonal electrodiagnostic changes) was treated with prednisone for Bell's palsy and IBD and PN symptoms improved although it could not be tolerated because of mania and weight gain. Patient 11 was also treated with methotrexate for IBD, which had no impact on the PN. The patient was later treated with IVIg and had a significant improvement of neuropathic pain, with decreased requirements of common neuropathic pain medications.

Ulcerative colitis patients 5–10 (with large-fibre sensorimotor axonal involvement by electrodiagnostic testing) had neuropathic pain treatment with several different agents (e.g. antidepressants, gabapentin). Responses to these agents were variable at different stages with different patients, from mild to good. Patient 10 was treated with prednisone, but developed side effects. Additionally, as can be seen in Table 3, patients 5, 7 and 8 were treated with IVIg. Patient 5 also had a mild response to prednisone and patient 7 had a mild response to methyl-prednisolone. Patients 5 and 8 had moderate responses to IVIg, while patient 7 had a mild response.

Discussion

In this study, we present the largest case series of PN in patients with IBD. Both demyelinating (30%) and non-demyelinating neuropathies were observed. Despite the intrinsic limitations of any retrospective study, the combined literature analysis allowed us to characterize the different PN phenotypes seen in IBD, which reflects the complex interaction between a variety of IBD effects on the nervous system: extra-intestinal inflammation, immune-mediated disorders, nutritional imbalances (malabsorption, weight loss, vitamin deficiencies) and drug-induced changes.

PN ranks among the most frequent neurological complications seen in IBD patients. In the two largest retrospective series, the incidence of peripheral neuropathy varied from 0.9 (Lossos *et al*., 1995) to 3.6% (Elsehety and Bertorini, 1997). Lossos *et al*. reported neuropathy in 1.9% of UC patients and only myelopathy, myopathy and myasthenia gravis in CD patients (0% incidence of neuropathy), while Elsehety and Bertorini reported neuropathy in up to 3.6% of CD patients (Elsehety and Bertorini, 1997). This difference might be explained by the systematic exclusion of all metronidazole-treated CD patients by Lossos *et al*., which could have excluded IBD-related PN (e.g. patients submitted to short courses or with significant motor involvement that was not metronidazole related). In fact, until recently all forms of neuropathy in CD patients treated with metronidazole were thought to result from this medication, since CD was not considered to be a cause of PN (Coxon and Pallis, 1976).

PN has been associated with other gastrointestinal diseases, such as celiac disease (Chin *et al*., 2003). Over a 2-year period, we have seen more patients with celiac disease and PN (approximately 72 patients) than patients with IBD and PN; however, conclusions about a higher incidence of celiac disease and PN cannot be established, given our close collaboration with an international expert in celiac disease and a possible referral bias.

The overall incidence of neurological complications in IBD may vary from 0.2% to 19.3% (Gendelman *et al*., 1982; Lossos *et al*., 1995; Elsehety and Bertorini, 1997). In our study, neurological disorders other than PN were observed in 67% of the CD and 53% of the UC patients with PN and included: small vessel disease, transient ischaemic attacks, transient diplopia, strokes and intracerebral haemorrhage, seizures, ocular myositis, Bell's palsy, bilateral optic neuritis, tremor, 'central serous retinopathy', migraine and sleep apnea.

Gender predominance of the PN in IBD patients

In the United States and Western Europe, UC has a prevalence of 70–150/100 000 and CD of 20–40/100 000 (Friedman and Blumberg, 2001). Women and men are equally affected (Friedman and Blumberg, 2001). Surprisingly, our study demonstrates a marked male predominance in both CD and UC: 78% and 73%. Despite the possibilities of selection bias or chance, undetected genetic susceptibility in men may be another possibility, since some CD variants may be associated with distinct manifestations such as weight loss (Tomer *et al*., 2003). Some studies, however, have reported that extra-intestinal manifestations may be more common in women and CD (Lakatos *et al*., 2003). Of note, despite the

overall male predominance in our series, demyelinating neuropathies were more common in women. Our literature review also supports this trend (Table 6).

The controversial metronidazole-related PN and the evolution of PN in IBD patients

'Neuropathy is not a feature of CD and we have found only one dubious reference to its occurrence' (Coxon and Pallis, 1976). This quotation from the 1970s summarizes the concept that prevailed until very recently: IBD is not a cause of neuropathy. In order to compare our results and to fully understand the spectrum of PN in IBD, a systematic literature review of all case reports and series of patients with PN and IBD (treated or not with metronidazole) was performed. We found 32 papers about PN in IBD patients not treated with metronidazole (Table 6), with a total of 23 CD patients with sensorimotor involvement, 15 with sensory and 39 with autonomic involvement, 15 UC patients with sensorimotor involvement and 74 patients with autonomic involvement, 14 papers (74 patients) about metronidazole-treated IBD patients with PN (Table 4) and finally 11 papers (13 patients) about PN in non-IBD patients secondary to metronidazole exposure (Table 5).

To our knowledge, there is only a single and small prospective study on IBD patients specifically designed to establish the incidence of PN, which was published only as an abstract (Crespi *et al*., 1994). In this study, Crespi *et al*. observed after 3 years that 18% of IBD patients developed R–R interval changes, indicating cardiovascular dysfunction; however, no patient developed clinical or electrodiagnostic evidence of PN. In other studies, paraesthesias were common in CD patients regardless of whether they were treated with metronidazole or not (Stahlberg *et al*., 1991). In this regard, Stahlberg *et al*. followed by clinical and electrodiagnostic evaluation three groups of patients with CD: CD not treated with metronidazole, CD patients on metronidazole and CD patients with prior metronidazole use. Paraesthesias and increased threshold for temperature (documented by QST) were equally frequent in the three groups. No clinical or electrodiagnostic features could differentiate the groups. Other studies have also observed early autonomic changes (Lindgren *et al*., 1991, 1993; Zincone *et al*., 1995; Straub *et al*., 1997). However, such autonomic changes may not

Table 4 *Demographic, clinical and neuropathy work-up in CD patients treated with metronidazole (literature review)*

Reference	Sex	Age*	Onset†	Clinical phenotype	NCS	MNDZ dose	Other remarks
Boyce	F	29	3	Sensory ataxic	SM axonal	2 g/d for 2 mo (100 g); partial resolution	
Bradley		33				2400 mg/d × 56 d (73 g)	
Coxon	F	60	40	Distal sensory	Sensory axonal	600 mg/d × 50 d (30.6 g)	Low vitamin B12 level
Gendelman	?	12–22	>0	Sensory			
Holdstock						1200 mg/d	
Karlsson	F	20		Sensory		1600 mg/d × 140 d (224 g)	
Lagueny	M	41	6 mo	Sensory	Sensory axonal	200 g over 6 months	Nerve biopsy: axonal + demyelination/remyelination
Larrodé	F	52		Distal SM	SM axonal	1 mo (1.5 g/d): slow resolution, complete?	
Said	F	26	1	Distal sensory	SM Axonal	13 mo (180 g); partial resolution	Nerve biopsy: decreased % of myelinated fibres
Said	M	45		Distal sensory	SM Axonal	15 mo (1 g/d); complete resolution	Nerve biopsy: 4% segmental demyelination
Ursing		26				1800 mg/d × 35 d (63 g)	
Ursing		24				1800 mg/d × 42 d (75.6)	
Case series							
Brandt							50% paraesthesias (13/26), *N* = 13
Duffy	6M/8F	12–22		Sensory (38% paraesthesias)		0–33 mg/kg × 4–11 mo (166 g)	54% abnormal sural conduction studies; 1 folate deficiency; *N* = 13
Stahlberg	7M/12F	23–62	3–23	21% paraesthesias		Max 800 mg/d; 236–1070 g	*N* = 19; Normal autonomic testing; 26% ↑ temperature threshold on QST
Stahlberg	5M/8F	19–72	3–24	39% paraesthesias		Max 800 mg/d; 402–2800 g	*N* = 13; MNDZ D/C prior 12 mo; 39% ↑ temperature threshold on QST
Ursing2							Paraesthesias in patients treated with sulphasalazline (*N* = 2) and MNDZ (*N* = 2)

F, female; M, male; Max, maximum; MNDZ, metronidazole; mo, months; QST, quantitative sensory testing; SM, sensorimotor PN.
*Age of neuropathy onset; †Time lag between IBD and neuropathy onset.

Table 5 *Demographic, clinical and neuropathy work-up in non-IBD patients treated with metronidazole (literature review)*

Reference	Disease	Sex	Age*	Clinical phenotype	MNDZ dose	Other remarks
Coxon	Abdominal abscess	M	40	Distal sensory	2400 mg/d × 48 d (114 g)	
Dubois	Lung abscess	M	52	Distal sensory	30 mg/kg/d (80 g) × 38 d	Nerve biopsy: segmental demyelination; CNS changes
Gastaut	''Infection''	M	28	Painful legs/moving toes	12 g	Vincristine, antineoplastic; ↓ myelinated fibres, regeneration
George	Anaerobic infection		49		2.2 g/d (128.8 g) × 58 d;	
George	Anaerobic infection		45		2.3 g/d (161.6 g) × 71 d;	
George	Anaerobic infection		48		2.2 g/d (19.9 g) × 9 d;	
Gupta	Amoebic abscess	M	25	Acute distal, axonal sensorimotor	400 mg TID for 15 d	Severe systemic disease
Hishon					210 d	
Kusumi	Mediast Abscess	F	45	Distal sensorimotor	1 g/d × 270 d (270 g)	Breast cancer; CNS changes
Ramsay	Endocrine ophthalm	F	43	Distal sensory	1200 mg/d for 99 d (114 g)	
Schipper	Cervix cancer	F	?	Sensory ataxic	3000 mg/d × 42 d (126 g)	Partial recovery; demyelinating changes
Takeuchi	Hepatic amoebiasis	M	67	Sensory/motor?	101.3 g	Resolution after discontinuation
You	Tonsillar abscess	F	35	Sensory/autonomic	2–3 g/d (116 g)	Septicaemia, fever

CNS, central nervous system; F, female; M, male; MNDZ, metronidazole.
*Age of neuropathy onset.

be easily interpreted since many IBD patients undergo colectomy or small bowel resection during the disease course, which may have a major impact on fluid homeostasis. CD patients had more prominent sympathetic involvement while UC patients had more pronounced cardiovagal dysfunction. Therefore, the earliest neuropathic manifestations in patients with IBD may be due to small fibre (autonomic or sensory)—with increased threshold to cold—or axonal sensory findings, which could be indistinguishable from pure, metronidazole-related PN. Additional evidence to support this statement can be inferred by comparing metronidazole-induced neuropathy in IBD (Table 4) and non-IBD patients (Table 5). As can be seen in Table 5, metronidazole-induced neuropathy in non-IBD patients (when not associated with other medical complications) is predominantly sensory, with partial or complete resolution after the drug discontinuation. The subgroup of patients without IBD, treated with long-term metronidazole (Table 5), was characterized by sensory phenomenology (with occasional sensory ataxic features) with or without complete resolution after discontinuation (Table 5). The minimum reported PN-related dose was 12 g (Gastaut, 1986). However, this patient also had malignancy and vincristine exposure. The patients with concomitant motor involvement had severe systemic disease, such as sepsis, anaerobic infections, malignancies and prolonged inpatient stays. In the two nerve biopsies in this group, segmental demyelination was seen in one case with encephalopathy and lung abscess, which could be secondary to another disease process rather than metronidazole.

In IBD patients treated with metronidazole (Table 4), a wider dose variation was observed: 30.6–2800 g. No clear dose-effect for PN was observed. A similar incidence of paraesthesias and increased threshold for temperature in metronidazole-treated and untreated patients suggested that these two forms of PN could not be easily distinguished (Stahlberg *et al*., 1991). In the CD patients treated with metronidazole (Table 4), the presence of motor involvement was scant, and in one patient was associated with B12 deficiency. Again, of the few patients who had nerve biopsy, mild segmental demyelination was seen in only one patient. However, in patients treated with metronidazole and PN, motor involvement was seen with a concomitant diagnosis of IBD or significant systemic involvement (critical illness with long duration of inpatient treatment).

In our study, pure sensory PN due to small fibre or sensory axonal involvement (painful PN or with mild ataxic and other negative sensory deficits) was common in both CD and UC patients. Few CD patients were previously treated with metronidazole. However, the disease progressed once this medication was stopped, which suggests a possible contributory role of metronidazole but not a determinant effect. Patients with restricted sensory involvement were younger than patients with concomitant involvement of motor and sensory large fibres. In addition, the interval duration between IBD onset and PN onset was much briefer in the patients with small fibre or sensory axonal involvement (in comparison to the sensorimotor large-fibre PN patients). These findings are in agreement with previous reports (see Tables 4 and 6), which suggests the earlier involvement of sensory fibres with IBD, which made it difficult to distinguish from metronidazole-related PN. In contrast to prior reports (Stahlberg *et al*., 1991), we did not observe a single case of documented autonomic neuropathy, despite the fact that few patients had autonomic complaints. This is probably explained by the fact that autonomic involvement is mild in IBD (e.g. no reported patient developed orthostatic hypotension). Our patients were not systematically screened for autonomic involvement and, therefore, minor autonomic changes could have been easily missed.

Table 6 *Demographic, clinical and neuropathy work-up in IBD patients not treated with metronidazole (literature review)*

Reference	Sex	Age*	Onset†	Clinical phenotype	Treatment response	Other remarks
Crohn's disease patients						
Barohn	?	?	?	CIDP		
Chaoui	F	17	0	Acute sensorimotor	Steroids	Nerve biopsy: axonal, secondary demyel; shock/parenteral nutrition
Coert	F	29	−1	Multifocal sensorimotor	Surgical nerve release: partial resolution	
Cohen	F	32	10	Brachial neuritis		
Contamin	M	16	6 mo	Sensory + myelopathy + myositis	Steroids; complete resolution	Folic acid deficiency
De La Fuente	F	34	4	AIDP	Plasmapheresis: partial response	Death; low vitamin B12
Gariballa	F	71	Simult	Acute sensorimotor	Steroids	Death on acute presentation
Humbert	M	52	1	Demyelinating sensorimotor	Plasmapheresis; partial resolution	Nerve biopsy: collagen + onion bulbs; skin vasculitis
Larrodé	F	37	?(acute)	Miller–Fisher (MF) like	B12 led to complete resolution?	Brainstem involvement
Lossos	M	33	−2	Sensory ataxic		Nerve biopsy: ↑collagen; folic acid deficiency
Moormann	F	65	acute	AIDP	Major improvement	
Moormann	F	45	33	Sensorimotor demyelinating	Prednisone; improvement	Also had granulomatous myositis
Nemni	M	58	12	Sensory ataxic	?	IgG + to Schwann cells
Nemni	F	28	10	Acute sensory	?	IgG + Schwann cells
Rankin	?	?	?	Mononeuritis multiplex		
Vinals	M	24	−5	MF + brachial neuritis	Plasmapheresis; partial response	
You	F	65	Simult	AIDP	IVIg; partial response	
You	F	48	33	Demyel SM + myositis	Steroids; partial response	
Case series						
Elsehety				6 axonal SM/1 mixed	Steroid; partial resolution	Nerve biopsy: axonal with secondary demyelination
Elsehety	2F	79		Neuropathy/myopathy	Steroid; partial resolution	1 axonal; 1 vasculitis
Lindgren	11M/22F	19–66	2–35	Autonomic neuropathy		*N* = 33, Autonomic dysfunction in 48%
Stahlberg	9M/2F	24–65	2–24	19% paraesthesias		*N* = 28, normal autonomic testing, 19%↑ temperature threshold on QST
Straub		15–60		Autonomic neuropathy		*N* = 21
Zincone				Autonomic neuropathy		*N* = 2, 8% of CD patients
Ulcerative colitis patients						
Blin	M	52	1	Axonal SM		Onset with sulphasalazine; slow acetylator
Chad	M	50	1	CIDP: perineuritis	No response	Nerve biopsy: neuritis
Couratier	M	50	>0	MMN	IVIg; complete resolution	
Greco	F	6	Acute	Acute axonal sensorimotor	Prednisone; complete resolution	Resolution of neurological and gastrointestinal symptoms
Konagaya	M	57	>0	CIDP?		↑ IgG/IgM; nerve biopsy: demyelination
Larrodé	M	51	12	Distal sensorimotor	Prednisone; partial resolution	
Larrodé	F	57	3	Sensory ataxic	Prednisone; partial resolution	Nerve biopsy: axonal changes and vasculitis?
Lossos‡	2M/1F	58–70	0.7–12	AIDP		?
Lossos	F	23	9	Mononeuritis multiplex	?	
Lossos	M	35	4	Bibrachial plexopathy	?	
Okayama	F	40	7	Mononeuritis multiplex	Steroids; partial resolution	Nerve biopsy: axonal > demyelinating
Roca	F	69	30	AIDP	IVIg; complete resolution	
Saito	F	56	>0	AIDP	Plasmapheresis; complete resolution	
Steiner	F	67	1.5	AIDP	Steroids; complete resolution	Onset after steroid taper

Table 6 *Continued*

Reference	Sex	Age*	Onset†	Clinical phenotype	Treatment response	Other remarks
Zimmerman	F	66	1	AIDP	Steroids, partial resolution	
Zimmerman	M	58	12	AIDP	Steroids, partial resolution	
Case series						
Lindgren	23M/17F	24–71	10–31	Autonomic neuropathy		Vagal dysfunction
Straub		21–70		Autonomic neuropathy		$N = 29$
Zincone				Autonomic neuropathy		$N = 5$, 31% of UC patients

AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; IVIg, intravenous immunoglobulin; MNDZ, metronidazole; SM, sensorimotor.
*Age of neuropathy onset; †Time lag between IBD and neuropathy onset; ‡No CD patients developed neuropathy in this retrospective study.

IBD-associated PN may be immune mediated and responsive to immuno modulatory therapy

In previous reports of IBD and neuropathy, often many contributory risk factors for neuropathy were present (e.g. B12 deficiency). However, our literature review (Table 6) revealed a disproportional number with demyelinating neuropathies. The onset of the demyelinating PN in relation to IBD activity was variable, which is evidenced by the large interval range in the gap between IBD onset and PN onset. This is also in agreement with prior reports, which showed that IBD patients had PN varying from the very first manifestation of PN to relapses of IBD (see Table 6).

Some of the patients whose symptoms of neuropathy improved had CIDP or MMN, which are known to improve with immunotherapy. The association of IBD and CIDP has been previously noted (Barohn *et al*., 1989). We identified IBD in only a minority of the 996 patients with CIDP seen at our centre. In addition to patients with CIDP and MMN, we also identified patients who had an axonal neuropathy associated with IBD that responded to immunotherapy. Though it is well known that a large number of patients with CIDP may not fulfil the AAN diagnostic criteria (Briani *et al*., 1996), which we used to identify patients, it is unlikely that all of these patients had CIDP. Even when we evaluated our patients using the recently proposed and more sensitive 'minimal electrodiagnostic criteria' (Magda *et al*., 2003), no additional patients were identified as having CIDP.

The literature review shows that most of the IBD patients responded to immunotherapy, which is also consistent with our current observation. In addition, IBD without 'demyelinating' markers in the nerve biopsies and electrodiagnostic studies also responded to immunomodulatory agents in much the same way in our series as in many reported cases/series. Indeed, two examples of non-demyelinating neuropathies had IgG anti-Schwann cell antibodies (Nemni *et al*., 1987).

Conclusions

This study presents the largest case series of PN in IBD. Despite the intrinsic limitations of any retrospective study (referral bias leading to complex epidemiological patterns, unblinded ascertainment of individual response to therapy) and considering that our patients were seen in a tertiary centre after multiple evaluations at different centres, the aid of an extensive, systematic, combined analysis of the literature enabled us to characterize the clinical and electrodiagnostic features of PN in patients with IBD. These clinical syndromes are diverse and most likely secondary to PN ascertainment at different stages of IBD evolution, but certainly include a high percentage of acquired demyelinating PN. In IBD, response to immunotherapy occurred as expected in demyelinating PN, but also in patients with nerve conduction studies and neuropathological findings characteristic of an axonal neuropathy. Therefore, despite the fact that our study is retrospective and not designed to establish causality between IBD and PN, it is likely that there is a primary immune-mediated neuropathy as an extra-intestinal disorder associated with IBD and not merely a co-occurrence with CIDP. Overall, men with IBD may be more susceptible to the development of PN than women. However, women may be more prone to demyelinating neuropathies.

References

Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991; 41: 617–18.

Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989; 46: 878–84.

Blin O, Sangla I, Jouglard J, Cottin C, Pellissier JF, Serratrice G. Axonal neuropathy and salazosulphapyridine: slow acetylator phenotype. Rev Neurol (Paris) 1992; 148: 154–6.

Boyce EG, Cookson ET, Bond WS. Persistent metronidazole-induced peripheral neuropathy. DICP 1990; 24: 19–21.

Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. Br Med J 1977; 2(6087): 610–11.

Brandt LJ, Bernstein LH, Boley SJ, Frank MS. Metronidazole therapy for perineal Crohn's disease: a follow-up study. Gastroenterology 1982; 83: 383–7.

Briani C, Brannagan TH, Trojaborg W, Latov N. Chronic inflammatory demyelinating polyneuropathy. Neuromuscul Disord 1996; 6: 311–25.

Chad DA, Smith TW, DeGirolami U, Hammer K. Perineuritis and ulcerative colitis. Neurology 1986; 36: 1377–9.

Chaoui F, Hellal H, Balamane M, Boudhane M, Mikol J, Masmoudi A. Colonic Crohn's disease complicated with peripheral neuropathy. Gastroenterol Clin Biol 1990; 14: 869–72.

Chin RL, Sander HW, Brannagan TH, Green PH, Hays AP, Alaedini A et al. Celiac neuropathy. Neurology 2003; 60: 1581–5.

Coert JH, Dellon AL. Neuropathy related to Crohn's disease treated by peripheral nerve decompression. Scand J Plast Reconstr Surg Hand Surg 2003; 37: 243–4.

Cohen MG, Webb J. Brachial neuritis with colitic arthritis. Ann Intern Med 1987; 106: 780–1.

Couratier P, Truong CT, Khalil M, Preux PM, Tarabaud F, Vallat JM. Cranial nerve palsies in a multifocal demyelinating neuropathy with persistent nerve block associated with hemorrhagic ulcerative colitis. Rev Neurol (Paris) 2000; 156: 179.

Contamin F, Ollat H, Lévy VG, Thierman-Duffaud D. Involvement of the peripheral and pyramidal nervous system in Crohn disease. Determining role of folic acid deficiency. Sem Hop 1983; 59: 1381–5.

Coxon A, Pallis CA. Metronidazole neuropathy. J Neurol Neurosurg Psychiatry 1976; 39: 403–5.

Crespi V, Bogliun G, Marzorati L, Zincone A, D'Angelo L, Liberani A et al. Inflammatory bowel disease and peripheral neuropathy. J Neurol 1994; 241 (Suppl 1): 63.

de la Fuente-Fernandez R, Rubio-Nazabal E, de la Iglesia-Martinez F. Guillain-Barre syndrome as an extraintestinal manifestation of Crohn's disease. Postgrad Med J 1995; 71: 437–8.

Dubois A, Raffanel C, Pignodel C, Janbon C, Marty-Double C, Balmes P. Acute cerebellar syndrome associated with sensory neuropathy in a patient treated with metronidazole. Presse Med 1983; 12: 1547–8.

Duffy LF, Daum F, Fisher SE, Selman J, Vishnubhakat SM, Aiges HW et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 1985; 88: 681–4.

Elsehety A, Bertorini TE. Neurologic and neuropsychiatric complications of Crohn's disease. South Med J 1997; 90: 606–10.

Friedman S, Blumberg RS. Inflammatory bowel disease. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 15th ed. McGraw-Hill Professional; 2001, Online edition.

Gariballa SE, Gunasekera NP. Bilateral foot drop, weight loss and rectal bleeding as an acute presentation of Crohn's disease. Postgrad Med J 1994; 70: 762–3.

Gastaut JL. Painful legs and moving toes. A drug-induced case. Rev Neurol (Paris) 1986; 142: 641–2.

Gendelman S, Present D, Janowitz HD. Neurological complications of inflammatory bowel disease. Gastroenterology 1982; 82: 1065.

George WL, Kirby BD, Sutter VL, Wheeler LA, Mulligan ME, Finegold SM. Intravenous metronidazole for treatment of infections involving anaerobic bacteria. Antimicrob Agents Chemother 1982; 21: 441–9.

Gondim FAA, Brannagan TH, Sander H, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. Neurology 2004; 62 (Suppl 5): A263.

Greco F, Pavone P, Falsaperla R, Sorge G. Peripheral neuropathy as first sign of ulcerative colitis in a child. J Clin Gastroenterol 2004; 38: 115–17.

Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine 1976; 55: 401–12.

Gupta BS, Baldwa S, Verma S, Gupta JB, Singhal A. Metronidazole induced neuropathy. Neurol India 2000; 48: 192–3.

Hishon S, Pilling J. Metronidazole neuropathy (letter). Br Med J 1977; 2: 832.

Holdstock DJ. Letter: Drug treatment in Crohn's disease. Lancet 1975; 2(7947): 1260.

Humbert P, Monnier G, Billerey C, Birgen C, Dupond JL. Polyneuropathy: an unusual extraintestinal manifestation of Crohn's disease. Acta Neurol Scand 1989; 80: 301–6.

Karlsson IJ, Hamlyn AN. Metronidazole neuropathy. Br Med J 1977; 3: 832.

Konagaya Y, Konagaya M, Takayanagi T. Chronic polyneuropathy and ulcerative colitis. Jpn J Med 1989; 28: 72–4.

Kusumi RK, Plouffe JF, Wyatt RH, Fass RJ. Central nervous system toxicity associated with metronidazole therapy. Ann Intern Med 1980; 93: 59–60.

Lagueny A, Vallat JM, Lamouliate H, Dubarry JJ. Sensory neuropathy and metronidazole. Apropos of a recent case with ultrastructural study. Sem Hop 1977; 53: 2207.

Lakatos L, Pandur T, David G, Balogh Z, Kuronya P, Tollas A et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World J Gastroenterol 2003; 9: 2300–7.

Larrodé P, Ramon Y Cajal S, Iniguez C, Sopena F, Gonzalez P, Morales F. Peripheral neuropathy associated with intestinal inflammatory disease. Neurologia 2001; 16: 133–7.

Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. Scand J Gastroenterol 1991; 26: 361–6.

Lindgren S, Stewenius J, Sjolund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol 1993; 28: 638–42.

Lossos A, Argov Z, Ackerman Z, Abramsky O. Peripheral neuropathy and folate deficiency as the first sign of Crohn's disease. J Clin Gastroenterol 1991; 13: 442–4.

Lossos A, River Y, Eliakim A, Steiner I. Neurologic aspects of inflammatory bowel disease. Neurology 1995; 45: 416–21.

Magda P, Latov N, Brannagan TH 3rd, Weimer LH, Chin RL, Sander HW. Comparison of electrodiagnostic abnormalities and criteria in a cohort of patients with chronic inflammatory demyelinating polyneuropathy. Arch Neurol 2003; 60: 1755–9.

McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fibre density: normative reference range and diagnostic efficiency. Arch Neurol 1998; 55: 1513–20.

Moormann B, Herath H, Mann O, Ferbert A. Involvement of the peripheral nervous system in Crohn's disease. Nervenarzt 1999; 70: 1107–11.

Nemni R, Fazio R, Corbo M, Sessa M, Comi G, Canal N. Peripheral neuropathy associated with Crohn's disease. Neurology 1987; 37: 1414–17.

Okayama R, Yamada M, Tamaki M, Orimo S, Arai M. Mononeuropathy multiplex with ulcerative colitis. Intern Med 1993; 32: 651–4.

Olney RK, Lewis RA, Putnam TD, Campellone JV Jr; American Association of Electrodiagnostic Medicine. Consensus criteria for the diagnosis of multifocal motor neuropathy. Muscle Nerve 2003; 27: 117–21.

Ramsay ID. Endocrine ophthalmopathy. Br Med J 1968; 4: 706.

Rankin GB, Watts HD, Melnyk CS, Kelley ML Jr. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. Gastroenterology. 1979; 77: 914–20.

Roca B, Moreno I, Meneu E. Ulcerative colitis and acquired demyelinating neuropathy (Guillain-Barré syndrome). Neth J Med 1999; 54: 129–30.

Said G, Goasguen J, Laverdant C. Neuropathy in long term treatment with metronidazole. Rev Neurol (Paris) 1978; 134: 515–21.

Saito M, Hozumi I, Kawakami A, Tsuji S. A case of post-rubella Guillain-Barre syndrome associated with ulcerative colitis. Rinsho Shinkeigaku 1994; 34: 1121–24 (abstract in English).

Schipper H, Beale FA, Bush RS, Fryer C. Metronidazole as a radiosensitizer (response). N Engl J Med 1976; 294: 901.

Stahlberg D, Barany F, Einarsson K, Ursing B, Elmqvist D, Persson A. Neurophysiologic studies of patients with Crohn's disease on long-term treatment with metronidazole. Scand J Gastroenterol 1991; 26: 219–24.

Steiner I, Wirguin I, Abramsky O. Appearance of Guillain-Barré syndrome in patients during corticosteroid treatment. J Neurol 1986; 233: 221–3.

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. J Neuroimmunol 1997; 80: 149–57.

Takeuchi H, Yamada A, Touge T, Miki H, Nishioka M, Hashimoto S. Metronidazole neuropathy: a case report. Jpn J Psychiatry Neurol 1988; 42: 291–5.

Tomer G, Ceballos C, Concepcion E, Benkov KJ. NOD2/CARD15 variants are associated with lower weight at diagnosis in children with Crohn's disease. Am J Gastroenterol 2003; 98: 2479–84.

Ursing B, Kamme C. Metronidazole for Crohn's disease. Lancet 1975 Apr 5; 1(7910): 775–7.

Ursing B, Alm T, Barany F, Bergelin I, Ganrot-Norlin K, Hoevels J et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. II. Result. Gastroenterology 1982; 83: 550–62.

Vinals M, Anciones B, Cruz Martinez A, Barreiro P. Recurrent Miller-Fisher syndrome associated with brachial neuritis. Neurologia 1989; 4: 61–5.

You B, Grilliat JP. Metronidazole neuropathy. Nouv Presse Med 1981; 10: 708.

Zimmerman J, Steiner I, Gavish D, Argov Z. Guillain-Barré syndrome: a possible extraintestinal manifestation of ulcerative colitis. J Clin Gastroenterol 1985; 7: 301–3.

Zincone A, Bogliun G, Crespi V, Marzorati L, D'Angelo L, Beretta L et al. Autonomic neuropathy in ulcerative colitis. Scand J Gastroenterol 1995; 30: 399–400.