Rare association of polyneuropathy and Crohn's disease: a clinicopathological study of 4 cases

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The purpose of this study is to investigate the clinical, electrophysiological and pathological features of neuropathy in patients with Crohn's disease.
Biopsies were selected from over 700 sural nerve biopsies. The diagnosis of Crohn's disease was based on established clinicopathological criteria. Complete laboratory, clinical, electrophysiological and pathological studies were performed in all cases.
Nerve biopsies of 4 patients were diagnosed as neuropathy and Crohn's disease. Distal symmetrical sensorimotor polyneuropathy was the pattern of neuropathy. The pathological features were mixed, demyelination with predominant axonal degeneration and a varying pattern of myelinated fiber loss. There were no vasculitic changes found.
We conclude that patients with Crohn's disease are complicated frequently with polyneuropathy, and as remission depends on immunosuppressive therapy, it is important to recognise it in the early stage. The diagnosis of polyneuropathy is based on clinical and electrophysiological studies, but precise histology, immunohistochemistry and morphometric studies of the peripheral nerve biopsy may be decisive in establishing the diagnosis.

Key words: Crohn's disease, polyneuropathy, axonal degeneration, demyelination.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease involving the gastrointestinal tract. The aetiology is unknown. Patients usually present with abdominal pain and diarrhoea, frequently accompanied by fever and weight loss. Extraintestinal complications of CD are common and include mainly arthritis, ocular, dermatologic manifestations and neurological abnormalities [1-4]. Peripheral neuropathy (PN) is one of the most frequent reported neurological complications in patients with CD [5-10]. As the peripheral nerve disease often dominates the clinical picture, the peripheral nerve biopsy may be very useful to establish the diagnosis. In fact, a few cases of CD with examination of the peripheral nerve biopsy have been published [11, 12].

The present retrospective study examines the clinical, electrophysiological, histopathological and morphometric features of 4 patients with CD in order to promote the early diagnosis of the neuropathy. Patients with CD are complicated frequently with polyneuropathy and it is important to recognise it, because the course of disease depends on immunosuppressive therapy introduced in the early stage.

Material and methods

Patient selection and clinical data

Biopsy specimens were selected from over 700 sural nerve biopsies performed at the Section of Neurology, Neurological Clinic of Athens University Hospital, during the last 20 years. The selection of patients was done according to the criteria for the diagnosis of CD [13]. Biopsies from patients with other causes of peripheral neuropathy such as malignancy, diabetes, vitamin B_{12} deficiency and metronidazole treatment

were excluded. All patients were referred to us for investigation of the polyneuropathy. Clinical data of the patients were obtained retrospectively from medical files. All patients had endoscopic, colonoscopic examination with biopsy, and a CT scan of the abdomen examinations done. Clinical severity classification was used according to the European Crohn's and Colitis Organisation (ECCO) [14]. Routine laboratory tests were performed in all cases at the time of diagnosis. Neurological interviews and examinations have been carried out in all patients prior to nerve biopsy by at least one neurologist. Muscle strength testing was scored in the 5 point Medical Research Council scale. The patients' functional state was estimated using the modified Rankin scale. Complete serological tests including CRP, C_3, C_4, ANA, ANCA, anti-DNA, RF, cryoglobulin, immunoelectrophoresis have been obtained in all cases. Serum and urine specimens were tested for monoclonal protein. CSF was investigated in all cases. Nerve conduction studies and electromyography (EMG) were performed in each patient at the EMG laboratory of our institution.

Neuropathy type was classified as mononeuritis multiplex, distal symmetrical sensorimotor polyneuropathy, or asymmetrical/overlapping neuropathy [15].

Histological techniques

Biopsy of the whole sural nerve was performed under local anaesthesia [16, 17]. Specimens were divided into three to five sections, each about 1 cm in length. One piece was fixed in 10% formaldehyde embedded in paraffin and cut transversely and longitudinally in sections of 7 μm thickness. The sections were stained with haematoxylin and eosin (HE). Another piece was fixed in Flemming's solution for 24 h, dehydrated in alcohol, embedded in paraffin wax and cut transversely and longitudinally in serial sections of 7 μm thickness. The sections were stained with Weigert Pall. A third piece was fixed in 1% glutaraldehyde, stained for 24 h in 1% osmium tetroxide, macerated in glycerol and then teased apart under a dissecting microscope in order to isolate single nerve fibers. At least 50 fibers were sampled and assessed for pathological conditions based on the criteria of Dyck *et al*. [18]. The specimens for semithin sections and electron microscopy were fixed in a solution of 2.5% glutaraldehyde in Sorenson buffer and embedded in epoxy resin. Semithin sections were stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead extract and examined with a Philips EM 201 electron microscope. Another portion of the nerve was prepared for immunohistochemical staining. Immunoperoxidase procedures were used for polyclonal antibodies IgG, IgM, IgA, C_3.

Pathologic changes were diagnosed and classified as predominantly axonal, demyelinating or mixed axonal and demyelinating based on both teased fibers and resin sections, according to established criteria [19].

Morphometry

Morphometric analysis of myelinated fibers was performed using VIDS III and OPTOMAX V image analysis system, connected with a microscope by a colour camera and included the measuring of the fascicle area, number, density and mean diameter of the myelinated fibers and fiber-size distribution histograms, myelin sheath thickness, mean axon diameter and g ratio (diameter of an axon without its myelin to the diameter of the axon with its myelin).

Results

Clinical features

Seven cases fulfilled the criteria for CD [13]. Three of them were excluded because there were other causes of peripheral neuropathy (one had a diagnosis of diabetes and vitamin B_{12} deficiency, one had vitamin B_{12} deficiency and one was treated with metronidazole). The final number of patients included in the study was four, 3 female and one man.

Abdominal pain, diarrhoea, anaemia, fever (37.2-37.5°C) and weight loss (> 5% body weight) were the most frequent clinical manifestations from the history of patients. There were no other extraintestinal symptoms or complications (obstruction, fistulae, or abscesses). There were no arthralgias or myalgias. Neuropathy symptoms began 10.3 ±2 years after CD onset. Neurological symptoms were mainly complaints in all patients during hospitalization in our department and all symptoms of CD were under control at presentation (except for episodes of mild diarrhoea in one of them). Routine haematological and biochemical showed mild anaemia in all of them. The cerebrospinal fluid showed mild protein increased in one of them (40 mg/100 ml). The clinical manifestations of the CD patients are summarized in Table I.

The age of neuropathy presentation in patients with CD was 50.4 ±2.1. The duration of the polyneuropathy before biopsy varied from 9 months to 21 months. All patients presented with sensory symptoms. There was severe hypoesthesia and paraesthesia in 1 and mild in 3 patients. Touch sensation was decreased in all patients. Mild distal muscle weakness was found in 3 and severe weakness in 1 patient, predominantly in the lower limbs. There were no signs of cranial neuropathy. No pronounced functional disability was found in any patient and the mean modified Rankin scale score was 3.46. Autonomic evaluation (Valsalva manoeuvre, deep breathing, tilting table and sympathetic skin-response testing) did not disclose any abnormality. There were no neurological disorders other than neuropathy.

Based on the clinical features, there was distal symmetrical sensorimotor neuropathy (1 of them with mild

Table I. Clinical manifestations of patients with Crohn's disease and polyneuropathy*

NO. OF CASE	AGE (YEARS)	SEX	PATTERN OF POLYNEUROPATHY	SYSTEMIC INVOLVEMENT				
				AP	DIARRHOEA	FEVER	MA	WL
1	48	M	ASP	+	+	+	+	+
2	51	M	SP	+	+	+	+	+
3	52	F	SP	+	+	+	+	–
4	56	M	SP	+	+	+	+	+

Pattern of polyneuropathy: ASP – asymmetrical polyneuropathy, SP – symmetrical polyneuropathy, AP – abdominal pain, MA – mild anaemia, WL – weight loss
**during hospitalization in our department all symptoms of Crohn's disease were under control at presentation*

asymmetries) in all cases. The electrophysiological studies were abnormal in all patients. All of them had mildly decreased motor and sensory conduction velocity with significantly reduced amplitude of the motor and sensory compound action potentials, without block or dispersion. The sural nerve action potential was absent in 1 patient. There was electromyographic evidence of chronic denervation in all patients and signs of active denervation in 1.

Histopathology

At least three fascicles were studied in each nerve biopsy.

Epineurial and endoneurial area: There was no evidence of vasculitis. Specifically, there were no significant vessel changes or inflammatory cells infiltrate. Qualitatively, the most prominent abnormality was that of basement membrane mild thickening.

Myelinated fibres: Characteristic finding in our study is the loss of fibers in all nerve biopsies. The analysis of the histopathological findings revealed a varying degree of loss of myelinated fibers of all diameters in all cases. Mixed axonal degeneration and demyelination appears in all cases but the axonal degeneration was the predominant characteristic. There were rare presentation of onion bulb formation in all of them.

Teased fibres: Segmental demyelination was the most frequent abnormality.

Immunohistochemistry: The immunohistochemical study was negative to antihuman polyclonal antibodies IgA, IgG, IgM, to C3 and fibrinogen.

Electron microscope: The ultrastructure study confirmed the axonal degeneration (focal accumulation of vesicles and axonal atrophy) and secondary demyelination.

Unmyelinated fibres: There was a decrease in the number of the unmyelinated fibres (morphometric study was not performed). Qualitative assessment of unmyelinated fibres demonstrated increased numbers of Schwann cell subunits devoid of axons and rare axonal sprouts suggestive of concomitant degeneration with mild regeneration.

Morphometry: Morphometric study revealed a significant loss of myelinated fibers (2512 ±1137) (compared with a published age-matched normal control, Jacobs 1985) [20]. The mean axonal diameter was decreased (2.77 ±0.68 μm).

The g ratio was markedly decreased (0.43 ±0.09) and supported the histopathological findings of mainly axonal involvement. The histograms of fibre diameter distributions confirmed the damage of all diameter fibers (Fig. 1).

Treatment: All patients received initial treatment with prednisone 60-80 mg (1 mg/kg day). However, follow-up was not sufficiently systematic so as to permit an accurate assessment of the response to treatment.

Discussion

Extra-intestinal manifestations occur in at least 25% of CD patients and they can occur prior to, in conjunction with, or subsequent to active bowel disease [1-3]. Multiple other organ systems can be affected, including the bones and joints, skin, eyes, hepatobiliary system, lungs, kidneys, central and peripheral nervous system.

The exact incidence of neurological complications is unknown, with reports varying from 0.2% to 35.7% [1, 2, 7, 8]. Peripheral neuropathy (PN) ranks among the most frequent neurological complications seen in CD patients. The incidence of peripheral neuropathy varied from 0.9% to 3.6% [7, 8]. This difference might be explained by the systematic exclusion of all metronidazole-treated CD patients by Lossos *et al.* [7]. In fact, until recently peripheral neuropathy in Crohn's disease has been described, to date, only with vitamin B_{12} deficiency or due to oral metronidazole treatment. 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 [21]. In our study three patients were excluded and have been attributed to other causes of neuropathy (one with diabetes and vitamin B_{12} deficiency, one with vitamin B_{12} deficiency and one with metronidazole therapy).

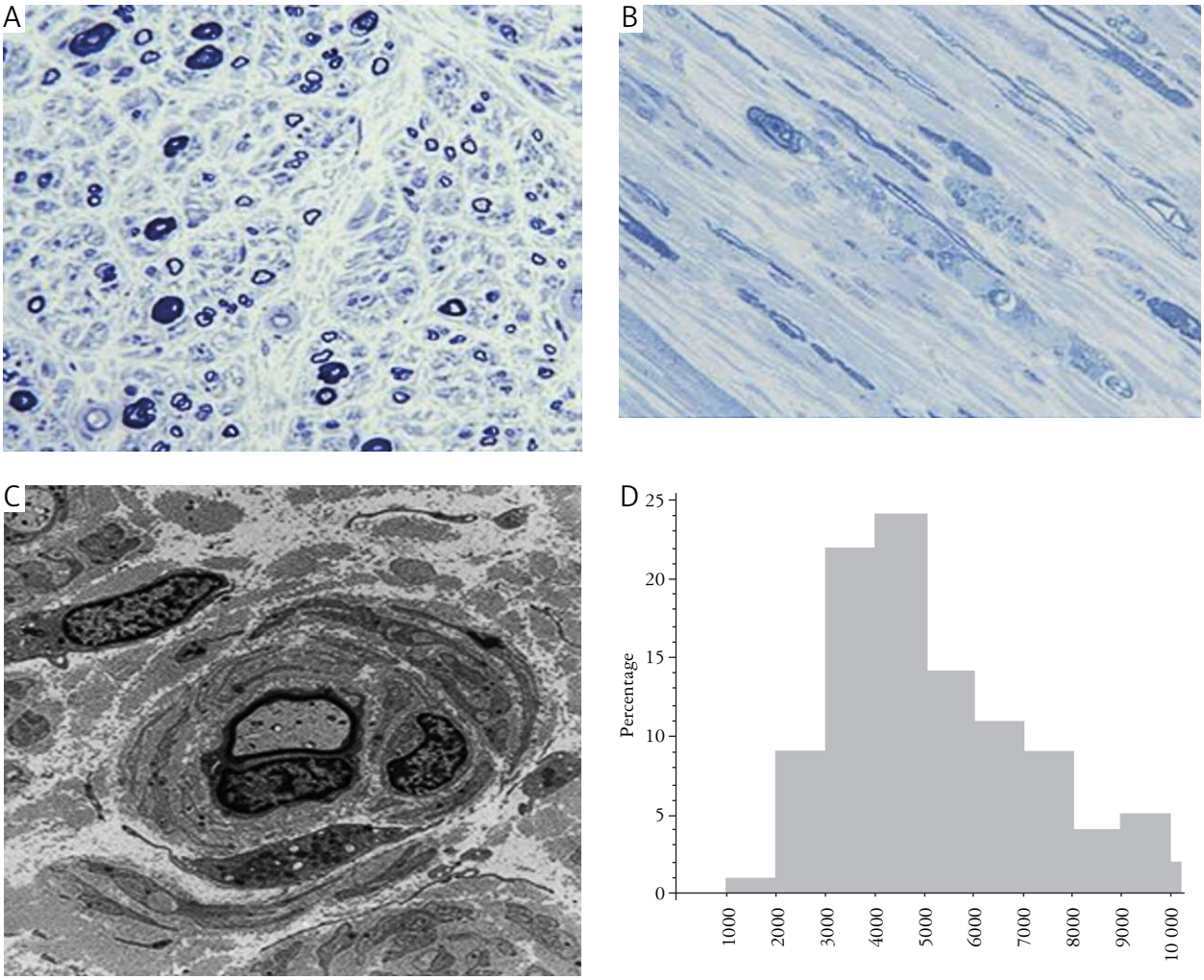

Fig. 1. Sural nerve biopsy findings: A, B – loss of myelinated nerve fibres (varying degree of loss of myelinated fibers of all diameters). Axonal degeneration. A few thinly myelinated fibers. Transverse and longitudinal sections. Toluidine blue staining. Magnification ×400; C – onion bulb seen with electron microscopy; D – histogram shows unimodal fibers distribution

Although neuropathy is a frequent neurological complication in CD patients, there have been only a few studies of CD neuropathy [5-10]. The number of reports with complete clinical, laboratory, immunological, electrophysiological and nerve biopsy investigation is small [11, 12].

The spectrum of clinical manifestations seen in our patients was similar to that of the published reports [5-12]. Abdominal pain, diarrhoea and anaemia were the most frequent clinical presentations. The age of neuropathy presentation in our patients was 50.4 ±2.1 and is similar to the study of Gondim *et al.* (51.7 ±2.6).

Lossos *et al.* described 4 categories of neurologic involvement in CD: peripheral neuropathy, myopathy or myoneural junction dysfunction, cerebrovascular disease, and myelopathy [7]. Other groups of investigators have also documented demyelinating processes, seizures, encephalopathy, restless legs syndrome, sensorineural hearing loss, sacral nerve involvement and a cauda equina syndrome in patients with inflammatory bowel disease [22-28].

Neurological manifestations in our patients were peripheral polyneuropathy and there were no central nervous system findings.

As mentioned, several different PN phenotypes have been described in CD patients. Based on clinical and electrophysiological features, distal symmetrical sensorimotor neuropathy (1 of them with mild asymmetries) occurred in all cases in our study. Although mononeuritis multiplex is thought to be the most frequent neuropathic manifestation of CD [5, 6], symmetrical and asymmetrical polyneuropathies [5, 6, 9, 10] have also been reported in a considerable proportion of patients. The high rate of symmetrical neuropathy in our patients could be possibly due to the delay between the initiation of symptoms and the clinical and neuropathological examination. At a later stage of the disease a primarily mononeuritis multiplex or asymmetric polyneuropathy could evolve towards a symmetrical picture by summation of multifocal lesions [17]. Boylu *et al.* reported a patient with CD and chronic inflammatory demyelinating polyneuropa-

thy [29]. In the largest study of Gondim *et al.* there were three patients who met the criteria for chronic inflammatory demyelinating polyneuropathy [10]. Fuente-Fernandez *et al.* reported a case who fulfilled clinical and electrophysiological criteria for an acute axonal form of Guillain-Barré syndrome [30]. Moormann *et al.*, described two patients with CD and Guillain-Barré syndrome and suggested that this complication could be regarded as a possible extraintestinal manifestation of CD [9]. There was no acute evidence of polyneuropathy in our patients and nerve biopsy investigation did not reveal inflammatory cells as well as in the cerebrospinal fluid there was no protein-cell dissociation. Another feature which may be found in patients with CD is autonomic nerve dysfunction. Lindgren *et al.* investigated 33 patients with CD and in spite of normal peripheral nerve function, almost half of the patients, 48% (16/33), showed signs of autonomic neuropathy [31]. The occurrence of AN was not related to the duration or severity of CD or to biochemical evidence of inflammation or malabsorption of vitamins and trace elements. Ohlsson *et al.* reported a patient with subclinical sympathetic neuropathy which appears early in the course of CD. In contrast to prior reports but in accordance to the study of Gondim, autonomic evaluation of our patients did not disclose any abnormality [10, 31].

The actual pathogenesis inciting the peripheral neuropathy in patients with CD is uncertain. In some cases, nutritional factors (vitamin B_{12} deficiency) have been responsible and in others the peripheral neuropathy referred as a complication of medications used in treatment, such as metronidazole, infliximab (Remicade), simvastatin etc. [7, 32-35]. These conditions were excluded in our patients. Frequently, the explanation is not so clear [36, 37]. According to Humbert *et al.*, polyneuropathy in CD may have an immunological basis [9]. The efficiency of plasma exchanges in some patients suggests an autoimmune basis and vasculitis with circulating immune complexes has been identified in others [9, 11]. The absence of any inflammatory cells and immunoglobulin deposits in the nerve biopsy of our patients cannot support but also cannot reject this hypothesis.

The analysis of the histopathological findings in our study revealed a varying degree of loss of myelinated fibers of all diameters in all cases and both axonal degeneration and demyelination were present in all cases. The dominant finding in sural nerve biopsies in the small reported studies was characterized by demyelination, axonal degeneration or both axonal degeneration and demyelination [9, 10]. Humbert *et al.* reported a patient with CD and polyneuropathy, whose nerve biopsy showed signs of regeneration, as a good prognostic feature [11]. Our study confirmed these findings, as there were signs of regeneration in all biopsies. If polyneuropathy is diagnosed early, initiation of early immunosuppressive treatment to prevent loss of nerve axons is recommended and so is the use of neuroprotective drugs [38].

Although the presence of aphthous ulcers, fissure ulcers, transmural inflammation, fistulas, lymphangiectasia, fibrous structuring and neural changes (abnormalities of the enteric nervous system are common and they have been called 'neuromatous lesions') is predominantly a feature of endoscopic mucosal biopsies, granulomas in histological sections are a key feature of CD. Rarely does the granulomatous inflammation affect extraintestinal sites, such as the skin, liver, lungs, eyes and ovaries. The nerve biopsy findings in our patients showed no specific lesions of mucosal biopsies, as inflammatory cells or granulomas. It is unknown whether this is due to a different pathogenic mechanism or more nerve biopsy sections should be studied, as it is recommended in vascular neuropathy.

In conclusion, our study confirms that 1) CD neuropathy is a condition that should also think rule out other causes of polyneuropathy when; 2) although CD polyneuropathy is rare, it is important to recognize it in the early stage because remission depends on the immunosuppressive therapy; 3) the diagnosis of polyneuropathy is based on clinical symptoms and electrophysiological studies, but precise histology, immunohistochemistry and morphometric study of the peripheral nerve biopsy may be decisive in establishing the diagnosis; 4) the presence of regeneration is a good prognostic feature diagnosed early, initiation of early treatment to prevent loss of nerve axons is recommended; 5) as the pathophysiology of neuropathy remains unknown, these findings could prove useful in the study of CD polyneuropathy but further studies are needed to identify parameters likely to be helpful in the diagnosis of early nerve damage.

The authors declare no conflict of interest.

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