

**ORIGINAL RESEARCH**

## NEUROLOGICAL MANIFESTATIONS IN INFLAMMATORY BOWEL DISEASE

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### ABSTRACT

#### Introduction

The purpose of this retrospective study was to report neurological manifestations noted in patients who were monitored for inflammatory bowel disease, in order to document the pathophysiological, clinical, progressive, and therapeutic characteristics of this entity.

#### Material and methods

We conducted a retrospective study on patients monitored -in the gastroenterology service in Ibn Sina Hospital in Rabat, Morocco- for inflammatory bowel disease from 1992 till 2013 and who developed neurological manifestations during its course. Patients with iatrogenic complications were excluded, as well as patients with cerebrovascular risk factors.

#### Results

There were 6 patients, 4 of whom have developed peripheral manifestations. Electromyography enabled the diagnosis to be made and the outcome was favorable with disappearance of clinical manifestations and normalization of the electromyography. The other 2 patients, monitored for Crohn's disease, developed ischemic stroke. Cerebral computed tomography angiography provided positive and topographic diagnosis. Two patients were admitted to specialized facilities.

#### Conclusion

Neurological manifestations in inflammatory bowel disease are rarely reported. Peripheral neuropathies and stroke remain the most common manifestations. The mechanisms of these manifestations are not clearly defined yet. Currently, we hypothesize the interaction of immune mediators.

**KEY WORDS:** Inflammatory bowel disease ; ischemic stroke ; peripheral neuropathies.

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#### INTRODUCTION :

The extraintestinal manifestations of inflammatory bowel disease (IBD) "Crohn's disease (CD) and ulcerative colitis (UC)" are common. These extraintestinal manifestations precede, accompany, or are independent of the underlying bowel disease. The most common are articular, ocular and cutaneous manifestations. The frequency of extraintestinal manifestations in patients with IBD varies between 6% and 47% [1].

Neurological manifestations remain rare. The real effect of these complications is unknown and varies, in the literature, between 0.25 and 35.7 %, which can be explained by the difference of the criteria of inclusion and selection of patients [2]. Most writings only reported clinical cases or small series of patients [3].

Through this retrospective study and a review of literature, we document the pathophysiological, clinical, progressive, and therapeutic characteristics of this entity.

## MATERIAL AND METHODS

This is a retrospective study conducted in the gastroenterology service « Medecine C » of Ibn-Sina Hospital in Rabat, between 1992 and 2013. The diagnosis of IBD was made on a series of clinical, biological, endoscopic and histological arguments. To identify the accountability of IBD in the development of neurological complications, we excluded patients with nutritional deficit and patients with cerebrovascular risk factors. We analyzed epidemiological data, results of clinical and para-clinical examinations, response to treatment and progression. Patients were divided according to the type of developed manifestations.

## RESULTS

In a total of 1050 patients monitored in our training for IBD, 6 patients developed neurological manifestations (Table 1): 4 men and 2 women, average age 41 years (range 28-55 years) at the moment of diagnosis. All our patients had Crohn's disease. Only one patient had another extra-intestinal manifestation. The remission of the digestive pathology was achieved through corticosteroids: prednisone or budesonide, with 5-aminosalicylates derivatives (Pentasa®, Salazopyrin®), immunosuppressants "azathioprine" and anti-TNF alpha "infliximab" (REMICADE®).

Two groups of patients were identified according to the raised neurological disorder:

1. Ischemic stroke: (patient 1 and 2): patient 1 had stroke lesions in the deep right middle cerebral artery territory and vertebrobasilar territory, while patient 2 developed ischemia in the left superficial middle cerebral artery territory. None of the two patients had cerebrovascular risk factors.

Case report (patient 1). Mr. D. M, 55, monitored since 2003 for ileocecal Crohn's disease diagnosed based on endoscopic, histological and progressive arguments. In 2009, the patient was admitted for left deficit. Neurological examination revealed a left hemiparesis with facial involvement and coordination disorder. Assessment of CT scan of the brain showed: ischemic stroke lesions in the deep right middle cerebral artery territory and vertebrobasilar territory. The patient received specialized care at medical neurology department and progressed well. The radiological assessment "CT scan complemented by MRI scan" made a year later, showed regression of old lesions.

2. Peripheral neuropathy (patient 3,4,5 and 6). All patients had Crohn's disease, 3 of whom developed acute neuropathies, while patient 4 had a chronic axonal neuropathy.

Case report (patient 3). Mr. B.M, 33, appendectomized in 1988, monitored since 1999 for ileocecal Crohn's disease, put under mesalamine plus corticosteroids, showed good evolution.

During the course of the disease, the patient showed:

- Anterior uveitis.
- Spondylarthropathy: put under salazopyrin®, showed good evolution.
- Acute pancreatitis induced by azathioprine.

In 2003, the patient showed flaccid paraplegia gradually worsening to reach the four limbs with a proximal predominance. Electromyography (EMG) showed: elongated distal motor latency; decreased motor conduction velocity and absence of F waves. The patient was initially put on carbamazepine, but was took off carbamazepine two weeks later following a drug eruption, and then placed under the combination: spastic "baclofen" + piracetam, the evolution was favorable with a decline of 8 years.

N	Age/Sex	Type of disease	Other manifestation	Interval	Neurological manifestations	Treatment	Evolution
1	55/M	Ileocecal Crohn's disease		72	Ischemic stroke	Neurological resuscitation	Favorable
2	35/M	Ileocecal Crohn's disease		60	Ischemic stroke	Neurological resuscitation	Death
3	33/M	Ileocecal Crohn's disease	Anterior uveitis. Spondylarthropathy	36	Chronic inflammatory demyelinating neuropathy	Antispastic + Piracetam	Favorable
4	28/F	Colonic Crohn's disease		18	Acute polyradiculoneuropathy	corticosteroids	Favorable
5	40/M	Ileocecal Crohn's disease		276	Acute motor-sensory axonal neuropathy		Favorable
6	39/F	Ileocecal Crohn's disease		72	Acute polyradiculoneuropathy		Favorable

**Table 1:** Characteristics of patients with neurological manifestations associated with IBD.

## DISCUSSION

Neurological manifestations are rarely reported in IBD. They can be contemporary or independent of its exacerbations. [4]

The occurrence of neurological manifestations varies in the literature between 2.7 p. 100 in the series of Lossos "1995" (5) and 33.2 p.100 in the series of Elsehethy (6). In Lossos' study on a group of 638 patients with IBD including 377 with Crohn's disease, patients with malabsorption of Vitamin B12 or folic acid were excluded, as well as patients treated on the long term with metronidazole.

Three categories of neurological manifestations have been described: peripheral neuropathy, stroke and demyelinating neuropathy.

1- Peripheral neuropathy: is the most common neurological complication and most reported in the literature (5, 6).

Several tables have described: Acute inflammatory demyelinating neuropathy (Guillain-Barré syndrome).

Acute motor-sensory axonal neuropathy. Brachial plexopathy. Mononeuritis. Cranial neuropathies.

Among the largest and most interesting series of patients with inflammatory bowel disease and a neuropathy is Gondim study "2005" (7), which has included 33 patients, 18 with Crohn's disease CD and 15 with Ulcerative colitis UC have developed peripheral neuropathies, after excluding other causes of these neurological manifestations. Gondim noticed a male predominance, the average age of the existence of these manifestations was 52 years. Demyelinating neuropathies increased in 28% of cases "5 patients," 2 with multifocal motor neuropathy, and 3 with chronic inflammatory demyelinating neuropathy. 11 patients (61%) had large-fiber axonal neuropathy (7 with damage of sensorimotor fibers, and 4 with damage of sensory fibers), while 2 (11%) were diagnosed with small fiber neuropathy. Symptoms of peripheral neuropathies start earlier in the evolution of CD than in that of UC. Patients with small fiber sensory neuropathy were younger than those who developed large-fiber neuropathy. 60% of patients received

immunotherapy, and showed good evolution at the end of treatment.

Myopathy was also described in the literature creating tables of polymyositis, dermatomyositis or subclinical myositis. Elsehety reported 4 cases of inflammatory myositis confirmed by muscle biopsy on 253 patients with CD, 2 of whom also had neurogenic damage. These manifestations decreased with corticosteroids.

2-Stroke: The incidence of stroke in IBD varies in the literature between 0.12 and 4.7% [5, 6,8]. All vascular territories can be damaged, venous thrombosis is the most frequent damage. [9]

3- Demyelinating neuropathy.

Other less common neurological tables showed: Seizures (often generalized than focal). Headaches. Neuropsychiatric manifestations (depressive syndromes, delusions) are occasionally reported in the literature [10]. The number of patients treated and monitored for IBD in the gastroenterology service "medicine C" in Ibn Sina Hospital in Rabat, between 1992 and 2011, is estimated at 1050 patients. Only 6 patients were reported in this study. Several causes can explain the limited number of patients who developed neurological manifestations. Firstly, the strict criteria of inclusion, also only patients with significant manifestations requiring care in hospitals were considered. Therefore, our study allows the assessment of only severe manifestations of the neurological system.

Until recently, neurological manifestations in IBD were attributed to the long-term treatment with metronidazole. The review of the literature, in 14 papers of which, «74 patients » treated with metronidazole during monitoring for IBD have developed neurological manifestations, in 11 papers, «13 non-IBD patients» treated with metronidazole developed peripheral neuropathies, and in 32 articles, «77 patients » developed peripheral neuropathies in IBD without receiving treatment with metronidazole [11, 12]. Currently, we instead hypothesize the interaction of complex effects of IBD on the nervous system:

1) Immune Disorder: bringing a massive response to ubiquitous antigens, due to vasculitis which may become complicated in the central nervous system by a stroke, and also in the peripheral nervous system. Two strong arguments support this hypothesis: First, most patients with IBD respond to immunotherapy, and even patients with no signs of demyelination in the nerve biopsy respond to immunomodulators. And also, the very frequent association with other autoimmune diseases: myasthenia, dermatomyositis.

2) Infectious cause: The occurrence of polyradiculoneuritis in a *Campylobacter jejuni* enteritis is currently well proven [13]. The autoimmune theory by molecular mimicry between lipopolysaccharide located on the bacteria envelope and gangliosides in the peripheral nervous system is the most accepted theory. In the study of ZHANG LI et al, there is a higher level of anti-*Campylobacter jejuni* antibody in children with Crohn's disease, and also its isolation in intestinal biopsies of these children. [14]

3) Hyperhomocysteinemia: hyperhomocysteinemia was observed in 89 of 171 patients with CD (52%). [15] The frequency of vascular complications of Crohn's disease [16] and the observation of higher plasma levels of prothrombotic factors (Factor VII: C, lipoprotein-a, fibrinogen, cardiolipin antibody) in Crohn's disease than in control populations emphasize the role of a prothrombotic state possible in this condition. [17]

4) Vitamin deficiency, secondary to malabsorption: folic acid and Vitamin B12. Neurological signs -especially combined sclerosis of the spinal cord - are associated with Vitamin B12 deficiency [18].

## CONCLUSION

In conclusion, peripheral neuropathies and ischemic stroke can have a genetic background and a common pathogenic mechanism with IBD. Prospective studies would best answer the question of the prevalence and occurrence of neurological manifestations in patients with IBD.

## AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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Declared none.

## PATIENT CONSENT

Written informed consent was obtained from patients for publication of this study.

## COMPETING INTERESTS

The authors declare no competing interests.

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