Gastrointestinal dysmotility complicating Behçet's syndrome: description of a newly recognised clinical phenotype

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Abstract

Objective

Gastrointestinal dysmotility may arise in a variety of auto-immune and auto-inflammatory diseases and hitherto has not been described in Behçet's syndrome (BS).

Methods

We present data on a cohort of seven patients under our care who presented with symptoms of and investigations compatible with an immune associated disorder of gastrointestinal motility, or enteric neuropathy.

Results

We describe the clinical features and investigation results. We undertook a trial of a novel treatment in the disease, apheresis, and noted a response not only to the enteric neuropathy but also to the systemic features of the disease, despite previous maximal immunosuppressive therapy in most cases.

Conclusion

Gastrointestinal dysmotility may arise in BS and is effectively treated by apheresis. The mechanism by which this response is made immunologically requires to be elucidated in future studies.

Key words

Behçet's syndrome, neurological, autoimmune gastrointestinal dysmotility, enteric neuropathy, apheresis

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Introduction

Behçet's syndrome (BS) is a systemic disease characterised by immune activation leading to a neutrophil response in affected tissues, in particular the oropharynx, gastrointestinal tract and genital region (1). Any tissue may be involved. It is an auto-inflammatory disease, and to date no antibody has been found to be associated with any clinical manifestation (2). Neurological complications, which arise in 10% of patients, comprise an inflammatory meningoencephalitis affecting the brain stem, brain and spinal cord in 70%; a cerebral venous sinus thrombosis in less than 20%; an arteritis leading to cerebral infarction, intraparenchymal or subarachnoid haemorrhage, aneurysm formation or arterial dissection; a focal or generalised myositis; and a peripheral neuropathy account for the remaining features (3).

Peripheral neuropathy in BS is most uncommon (1% of a series of 1031 cases) (4); most have axonal sensorimotor neuropathies, without evidence for inflammation, demyelination or vasculitis. However asymptomatic electrophysiological abnormalities are detected in 14–19% of unselected patients with the systemic disease without neurological complications.

In this paper we describe the clinical features and investigation results of a series of patients with gastroenterological symptoms compatible with the diagnosis of enteric neuropathy and recount their response to treatment with a novel therapy in BS, plasma exchange.

Patients and methods

All were patients attending the clinics of the BS centre of excellence. The BS centre of excellence is a national referral centre within the UK with three sites, which was founded in 2012. We have 2250 patients under regular review in total, 990 at the Royal London Hospital site. Patients are reviewed by a multidisciplinary team comprising experts in oral medicine, immunology, rheumatology, ophthalmology, neurology and nursing. The neurological and gastrointestinal features were evaluated by one of us (DK) and ES scored the BDCAF (5). Isotope imaging investigations were carried out at Royal Free Hospital by MH; patients were fed 12MBq ^{99m}Tc Nanocolloid mixed with mashed potato orally. This was found to be stable and acceptable to all patient groups. Images were then acquired dynamically for one hour using a low energy all-purpose collimator. The results were analysed to provide a time-activity curve showing the pattern of emptying along with an estimated half-emptying time. Gastrointestinal imaging was carried out in referring hospitals and imported for review. Neurophysiological studies of large and small fibre nerves were carried out by Consultant Clinical Neurophysiologists at the department of neurophysiology, Royal Free Hospital. Centrifugal apheresis using Spectra Optia centrifugation machines within the haematology department of the Royal Free Hospital was carried out and supervised by HK. We did not seek ethical approval for the study since we were devising an optimum treatment plan clinically not through research.

Clinical features

We have identified seven patients within our cohort with gastrointestinal symptoms who, following investigation, were diagnosed with gastrointestinal dysmotility. The clinical features in each case were of the mucocutaneous form of the disease; one had had venous thrombosis and in three other the joints had been prominently affected. Each had already been diagnosed and the gastrointestinal disorder had developed during treatment with immune suppression in each case. All underwent a series of blood and serological investigations (Table I) and each was normal aside from a speckled pattern antinuclear antibody in patient 1.

Patients 2 and 5-7 underwent cardiovascular autonomic function tests in the autonomic unit of the National Hospital and each was normal. Patient 5 was found to have an axonal peripheral neuropathy which did not deteriorate. The others had had normal nerve conduction studies.

All had undergone investigations within the gastroenterology departments of other hospitals; all had undergone endocopic evaluations, patients 1-4 and

Table I. Clinical details and response to treatment in the seven patients studied.

Patient (age, gender)	Systemic features	Duration of disease	Previous treatment	Clinical features	Imaging features	Blood investigations	Treatment outcome
1 (33, female)	MC, joints	19	S, Aza	Subacute gastroparesis	Gastroparesis	ANA + speckled	Normal diet
2 (42, male)	MC, e nod	23	S, Aza, ADA	Subacute gastroparesis, Jejunal intussusception	Gastroparesis + Intussusception	Normal	Normal diet; no further obstruction
3 (46, female)	MC, joints	26	S, MMF, IFX, ADA	Subacute gastric dysmotility with intragastric reflux	Gastroparesis	Normal	Soft diet
4 (51, female)	MC, joints	32	S, Aza, ADA	Colorectal intussusception without gastroparesis	Intussusception	Normal	No further obstruction
5 52, female)	MC highly active	36	S, Aza, Cy A, IFX, ADA	Chronic gastroparesis slow large bowel transit	Gastroparesis	Normal	Soft diet
6 (57, female)	MC, DVT and PE	34	S, Aza	Chronic gastroparesis, slow large bowel transit	Gastroparesis	Normal	Normal diet
7 (70, female)	MC, joints	48	S, Aza, IFX, ADA	Chronic gastroparesis, slow large bowel transit	Gastroparesis	Normal	Normal diet

Blood investigations: FBC, ESR, biochemical screening, thyroid function, vitamin B12 and folate, glucose and HbA1C, ANA, DNA, ENA, neuronal antibodies, α3 ganglionic acetylcholine receptor antibody, potassium channel antibody, anti-gliaden antibody.
MC: symptoms of the mucocutaneous form of the disease which included in each case orogenital ulceration and recurrent skins lesions. None exhibited pathergy.
DVT: deep vein thrombosis; PE: pulmonary embolism; e nod: erythema nodosum; S: corticosteroids; Aza: azathioprine; MMF: mycophenolate; Cy A: cyclosporine A; IFX: infliximab; ADA: adalimumab.

6 and 7 had undergone abdominal MR imaging and patients 1, 2 and 6 had been assessed and diagnosed in the neurogastroenterology departments of other London hospitals. These investigations were not repeated but their results scrutinised by us subsequently. Faecal calprotectin levels were assayed, and each was normal. None had been found to have gastrointestinal involvement by BS or other inflammatory bowel disease.

Under our care five underwent gastric emptying studies (Fig. 1); three were abnormal, one normal and one showed abnormal gastric emptying with intragastric reflux back from the duodenum, compatible with dysmotility.

Subacute disorder

Patients 1-3 had a subacute increasing disorder of dysmotility some years after the onset of the systemic disease and whilst taking treatment. The symptoms of patients 1 and 3 were so severe that they required PEJ and NG feeding to maintain weight, patient 2 had an associated jejunal intussusception identified on MR imaging leading to episodes of abdominal pain and features of subacute bowel obstruction and could only tolerate a soft diet.

Chronic disorder

Patient 4 had a gradual onset of obstructive gastrointestinal symptoms culminating in episodes of abdominal pain with distension due to gaseous entrapment requiring repeated hospitalisation and consideration of surgery. She was seen to have a colorectal intussusception on dynamic MR enterography. Patients 5-7 had a more gradual onset during their systemic disease of increasing problems with poor gastric emptying and slow large bowel transit which never became acute or severe and which continued for years.

Response of the gastrointestinal disorder to apheresis

Treatment with apheresis led in each case to an improvement in their disorder, the removal of the need for enteral feeding in patients 1 and 3, and no further hospitalisations for suspected bowel obstruction in patients 2 and 4. Those with more chronic symptoms noted an improvement in their symptoms with no further episodes of vomiting and more predictable and comfortable defaecation.

Response of the systemic features to apheresis

All patients had received treatment with steroids and immunosuppression compatible with the clinical course and disease severity. Five were receiving TNF-α antagonists in addition. The systemic disease had been deemed to be under stable control prior to initiation of treatment with apheresis. It was notable that following apheresis the systemic features all improved in addition; there was a reduction in the frequency of bouts of orogenital ulceration, less severe skin and joint manifestations, and an improvement in fatigue. Figure 2 shows the change in BDCAF in each patient before apheresis and following six months of treatment with apheresis.

Discussion

Chronic intestinal pseudo-obstruction (CIPO) is a disorder of gastrointestinal motility due to a disorder of peristaltic muscle or of the enteric nervous system which is uncommon, progressive leading to gastrointestinal failure in the majority, and of unknown aetiology. Any part of the gut may be affected, leading to achalasia, gastroparesis, small and large bowel dysmotility (6, 7). Both myopathic and neuropathic forms may be inherited.

Neuropathic causes are associated with degeneration of intramural neural cells, and a reduction in interstitial cells of Cahal, and in others evidence for inflammation within mesenteric ganglion cells (8) which may be lymphocytic or eosinophilic (9).

It occurs in mitochondrial neurogastro-

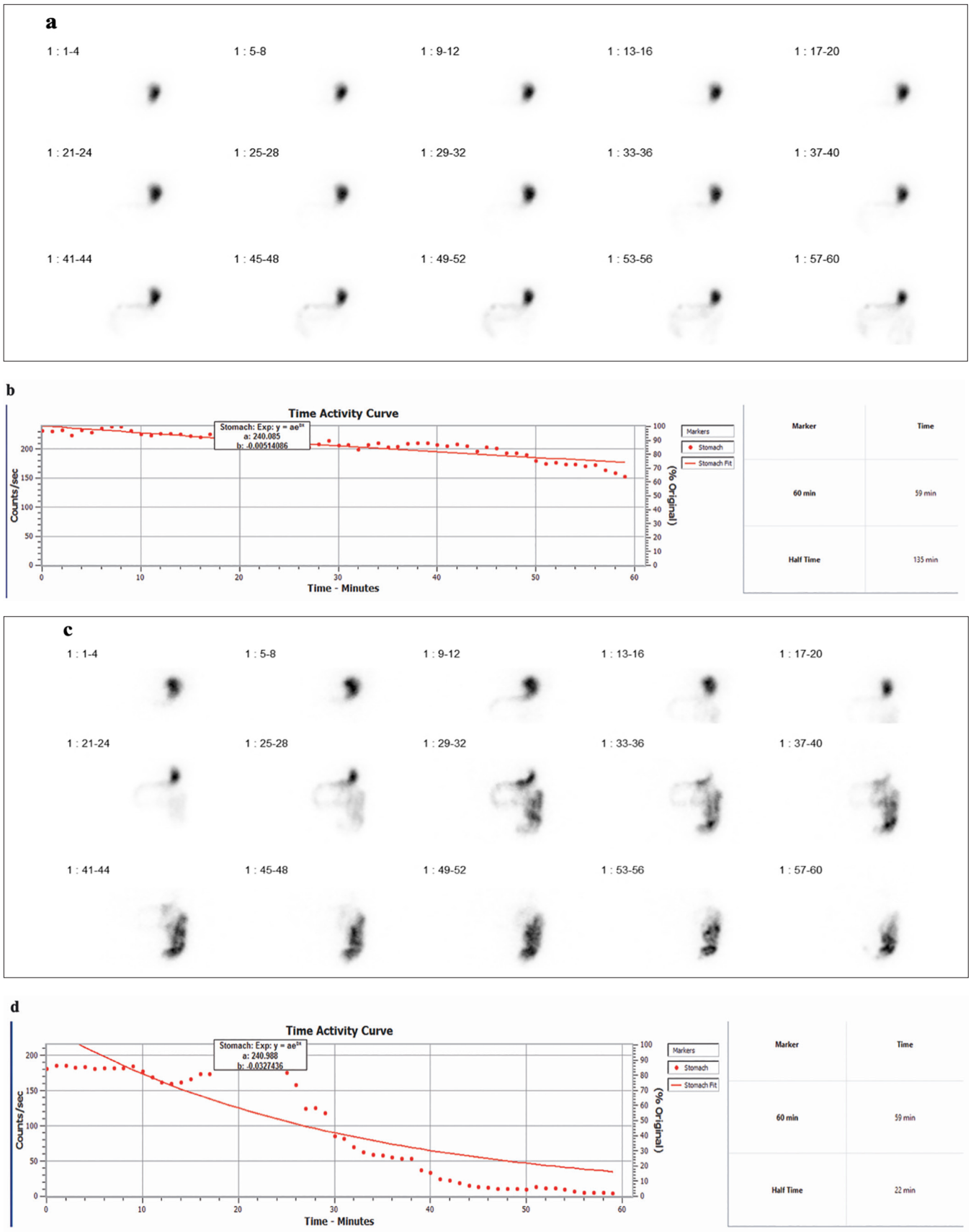

Fig. 1. Gastric emptying studies before and after treatment in patient 1.
a: Baseline gastric emptying showing little clearance from the stomach over 1 hour. **b**: Baseline data expressed as a time-activity curve giving a half-emptying time of 135 minutes. **c**: After treatment gastric emptying showing normal clearance of tracer from the stomach into the small bowel. **d**: After treatment data expressed as a time-activity curve giving a half-emptying time of 22 minutes.

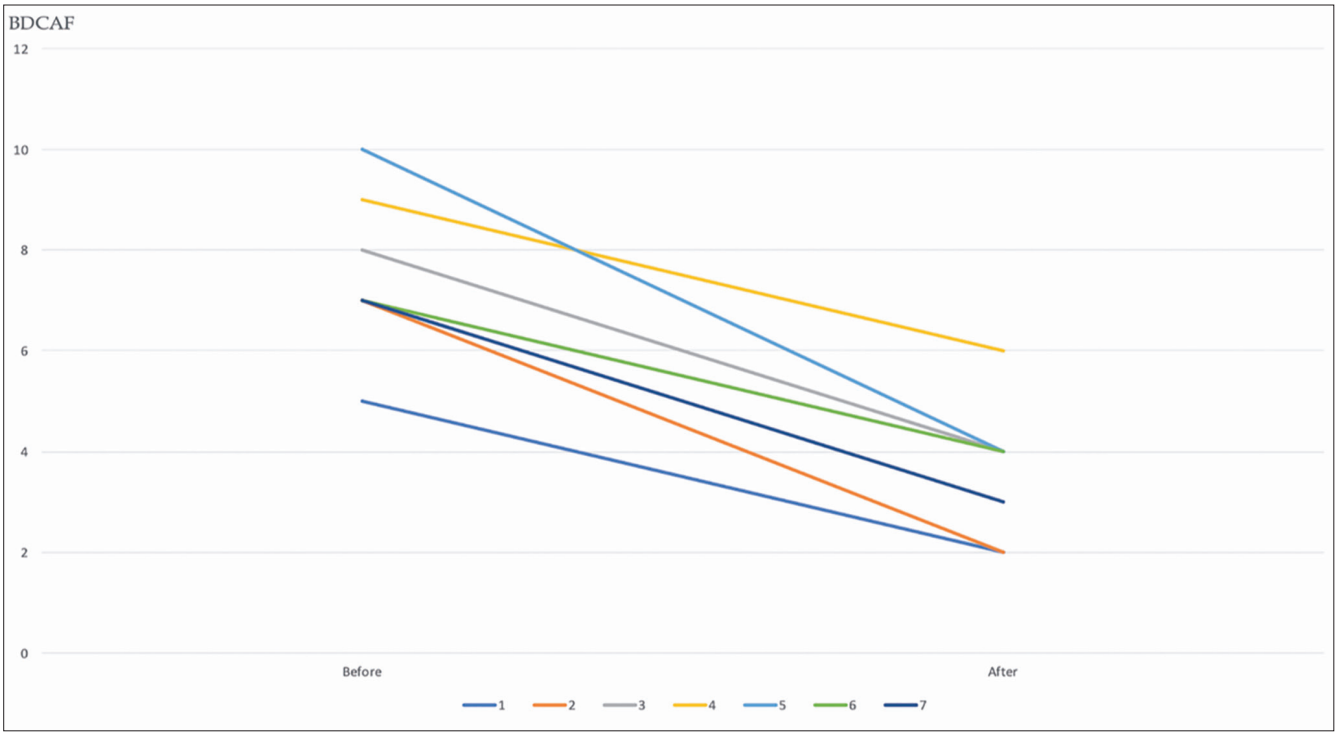

Fig. 2. Behçet's disease current activity form (BDCAF) score in each patient prior to and after six months of treatment with apheresis.

intestinal encephalomyopathy (in which it has a neuropathic aetiology), and neurodegenerative disorders. Amyloid deposits destroy myenteric ganglia. It may complicate Guillain Barré syndrome, a series of viral infections, Kawasaki syndrome, strongyloidiasis and Chagas' disease.

No treatment is known to be helpful, and nutritional support is given (7, 10) with symptomatic relief with acetylcholinesterase inhibitors, erythromycin and metoclopramide.

In scleroderma, gastrointestinal dysmotility occurs in the majority of patients (11, 12); it is thought that hypoperfusion of the myenteric nerves leads to smooth muscle atrophy and there is no evidence for an inflammatory ganglionitis (11). In systemic lupus erythematosus (SLE) it occurs in 2% of patients and is associated with disease activity and the presence of DNA and ENA antibodies (13-15). The histopathology is of an inflammatory myositis within the *muscularis propria* (17, 18) with preservation of the myenteric plexus (18). Patients respond to steroids and high dose immune suppression (15, 16); without treatment the smooth muscle is replaced by fibrous tissue (17).

Enteric neuropathy, or auto-immune gastrointestinal dysmotility (AGID), may arise isolated to the gastrointestinal tract or in association with more widespread autonomic dysfunction (18). 70% of cases have neural-specific auto-antibodies (19); 50% is associated with cancer (20).

In the only series in which treatment has been described 23 patients received either IVIg or intravenous methylprednisolone (19); 17 noted an improvement in symptoms or scintigraphic studies. 12 had neural specific antibodies and five did not. Six did not respond and no difference in clinical or laboratory feature was noted in comparison with those who did.

Plasmapheresis involves the separation of plasma from the cellular constituents of blood through filtration or centrifugation, with plasma replacement thereafter. In this way immunoglobulins, immune complexes and immune mediators such as cytokines and complement are removed from the blood. Antibody levels reduce by 50-75% up to three months after each exchange (21, 22) but there may be immune reactivation thereafter. Since BS is not known to be an antibody-associated disease and patients with the disease were treated with steroids and immune suppression already we considered apheresis a reasonable additional treatment, the concept being that the disorder might be associated with immune activation, that there may be circulating immune complexes and cytokines driving it and that there was a low risk of adverse events with this form of therapy.

In this series seven patients are described whose clinical features and investigations results suggest a disorder of intestinal motility. None had an antibody associated with the disorder of enteric neuropathy and only one had a more widespread disorder of the nervous system. Each improved with treatment, but those with a more recent onset and more severe symptoms improved proportionately more, implying a treatment responsiveness in early stages.

We do not have a histopathological examination, so we cannot define if the disorder is related to a myenteric ganglionitis or, like SLE, to an inflammatory myositis, but it is striking that a response to apheresis was made even in those who deteriorated despite maximal therapy with steroids, immune suppression and TNF-α antagonists. Like SLE, it appears to be a systemic rather than a local effect (there is no report of chronic intestinal pseudo-obstruction

in inflammatory bowel disease) caused by damage to the myenteric plexus or the *muscularis propria* by ulceration.

We noted an improvement in the severity of the systemic symptoms; five patients were taking TNF-α blockers and on apheresis we stopped this form of treatment; their improvement in clinical state continued and indeed improved further (Fig. 2). This suggests that removal of circulating products of immune activation provokes improvements in the systemic features of the disease as well, and that it proportionately greater than the effect of steroids, immunosuppression and TNF-α blockade. The pathophysiology of this effect should be defined in future studies.

In conclusion we have characterised the uncommon occurrence of gastrointestinal dysmotility in BS leading to gastroparesis and slow colonic transit times, which may develop slowly and progressively, or more subacute and more severely, which responds to a novel therapy in BS, plasma exchange, which proffers benefits not only in the gastrointestinal disorder but the systemic features of the auto-inflammatory disease itself.

Take home messages

1. Gastrointestinal dysmotility has not previously been characterised in BS.
2. We have identified both subacute and chronic clinical courses.
3. The disorder has arisen during treatment of the systemic disease.
4. A novel form of treatment in BS, apheresis, has been shown to be helpful in all cases, not only in the neurogastrointestinal disorder but also in the systemic disease, even in those already taking TNF-α antagonists.

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