

TITLE

Recognising and treating complicated fissuring perianal Crohn's Disease: a South-East Scotland cohort study.

SHORT TITLE

Recognising and treating complicated fissuring perianal Crohn's Disease

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AUTHOR CONTRIBUTIONS

Dr Christopher Burgess was involved in the conception and design of the study, data collection, data analysis, wrote the original and subsequent revisions of the manuscript, and approved the final manuscript.

Mrs Claire Clark, Cher Khedim, Katherine Armstrong and Dr Paul Henderson were involved in data collection, provided critical review of original and subsequent manuscript drafts, and approved the final manuscript.

Professor David Wilson serves as guarantor of the article, acquired all funding, conceptualized and supervised this study, was involved in data collection, provided critical review of original and subsequent manuscript drafts, and approved the final manuscript.

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UNSTRUCTURED ABSTRACT

Fissuring perianal Crohn's Disease (CD) is not recognised as a perianal phenotype in Montreal/Paris inflammatory bowel disease classifications however can occasionally present as complicated disease with severe perianal pain driving increasingly intensive medical therapy despite well controlled luminal disease. We identified a regional cohort of prospectively acquired incident cases of paediatric CD diagnosed <16 years of age in South-East Scotland over a 19-year period (1999 – 2018), and conducted a retrospective review of complicated fissuring perianal CD causing severe pain related to anal sphincter complex spasm at defecation. 247 new cases of paediatric CD were diagnosed with complicated fissuring perianal disease identified in 4 described cases (cumulative incidence 1.6%). These patients with marked fissuring and refractory anal sphincter complex spasm required neurostimulation-guided, four quadrant, anal intrasphincteric botulinum toxin. All experienced immediate success, measured by cessation of spasms, with variable ongoing symptom relief after median (range) 3 (2-5) BT injections.

KEYWORDS

Epidemiology

Paediatric

Anal fissure

Crohn's disease

Inflammatory bowel disease

INTRODUCTION

Fissuring perianal Crohn's disease (CD) is not currently recognised as a distinct perianal phenotype in either the Montreal¹ or Paris² classifications of Inflammatory Bowel Disease (IBD), instead categorized together with other non-penetrating and conservatively managed perianal lesions such as haemorrhoids and skin tags. This supports the assumption that discomfort associated with fissures is rarely debilitating and that they often heal completely with minor medical therapy^{3,14}. In contrast, penetrating fistulas have been identified as a poor prognostic marker at all ages, requiring intense multidisciplinary team management and early commencement of biological therapy³⁻⁸.

Perianal fissures are common in CD, reported to occur in up to 51% of patients⁹. Unlike the typical fissures resulting from constipation, which are often asymptomatic, self-limiting and primarily managed conservatively, patients with CD can develop fissures which are multiple, large, irregular and located laterally^{10,11}. We report 4 case studies of patients with complicated perianal fissures and sphincteric involvement requiring operative intervention to highlight the cumulative incidence and potential severity of complicated fissuring disease. We also describe the use of neurostimulation-guided, four quadrant, anal intrasphincteric botulinum toxin (BT) injection as an intervention that may be helpful in early symptomatic management and which can delay or even in the short- to medium-term avoid further surgery.

METHODS

Cohort

A regional South-East Scotland cohort of prospectively acquired incident cases of paediatric CD (diagnosed less than 16 years of age) was captured over a 19-year period (01.03.1999 – 28.02.2018). Cases were ascertained from multiple sources and validated via review of individual case notes to ensure they met CD diagnostic guidelines according to the revised Porto criteria¹³. Detailed phenotypic information was collected at diagnosis according to the Paris classification², with strict use of the 'p' descriptor limited to perianal fistula, anal canal ulcer or abscess. Complicated fissuring perianal CD was documented separately, defined as any fissuring perianal CD with both sphincteric involvement (resulting in sudden onset and protracted severe perianal pain due to anal sphincter complex spasm at defecation) and requiring operative management (due to failure to respond to standard topical therapy or simple analgesia).

Details of injection procedure

Neurostimulation-guided, four quadrant, anal intrasphincteric botulinum toxin (BT) injection was performed by a single paediatric surgeon as part of a formal perianal examination under general anaesthesia (EUA). BT (100 IU/ml concentration) was drawn up into labelled 1mL syringes to a dose of 6-7 units/kg (maximum 300 IU), with a further 1mL 0.9% Sodium Chloride flush to account for dead space within the giving set. A 22G x 50mm dual channel needle electrode (UniPlex NanoLine, Pajunk®, Geisingen, Germany) was attached to the nerve stimulator (Stimuplex® HNS 11, Braun, Hessen, Germany) and set to maximum frequency 2 Hz and maximum intensity 5 mA. The needle was then inserted at a 90-degree angle to the skin in 4 circumferential injection sites around the anus. BT was injected evenly,

divided into 4 quadrants, at the depth where an anal twitch indicates the intersphincteric plane. If an anal twitch was not visible a finger could be inserted into the anus to better determine the point of maximal stimulation of the anal sphincter complex; anal retraction was avoided to minimize sphincter disruption. A minimum interval of 4-6 months between injections was planned, although could be shortened at the discretion of the treating team. All patients were counselled on the potential risk of faecal incontinence as part of informed consent and prescribed stool softening medication post-procedure.

Statistics

Cumulative incidence of complicated fissuring perianal CD was calculated as the number of new cases divided by the total number of individuals in the population at risk. The specified time period for cumulative incidence included 1300 person years follow-up from date of diagnosis until discharge from paediatric services or end of study (31.05.2020). Statistical analysis was performed using the epitools package in R version 3.4.0 (R Foundation for statistical computing, Vienna, Austria). Ethical approval was not required for this observational study of service delivery in which clinical data was collected as part of routine patient care.

RESULTS

Cohort Characteristics

In total 247 new cases of paediatric CD (<16yrs) were diagnosed within the 19-year study period. Disease behaviour phenotype at diagnosis demonstrated 36/247 (15%) patients met strict criteria for the p descriptor. Only 1/247 patients (0.4%) was identified to have complicated fissuring perianal CD at diagnosis with a cumulative incidence of 4/247 (1.6%) over 1300 person-years follow-up. All four patients were female and diagnosed at a median age (range) of 9.9 (5.1-13.1) years. None of the cases adequately responded to simple analgesia or standard topical therapies (Box 1). 3 (75%) patients had been commenced on anti-tumour necrosis factor (anti-TNF) biologic prior to BT; all had adalimumab (ADA) and/or infliximab (IFX) and combination immunomodulatory therapy by study end.

Botulinum Toxin Injection

Nerve stimulator-guided, four quadrant, anal intrasphincteric BT was first injected at a median (range) of 22 (0-49) months after diagnosis. Success of BT was measured by cessation of anal sphincter complex spasm and all 4 patients had immediate and complete symptom relief following the first injection. The median (range) number of BT injections performed on each patient was 3 (2-5). Duration between injections was median (range) 5.3 (3.5-18) months. Side effects of neurostimulation-guided BT injections were minimal with a single episode of faecal incontinence reported after the first injection in 1 case only. Escalation of therapy to a diverting ileostomy was required for 1 patient due to decreasing levels of effectiveness after 5 BT injections over 2.6 years.

Index Case

Our first case presented at 7 years of age with superficial perianal fissuring, skin tags and discomfort that continued to worsen despite simple analgesia and topical anaesthetic gel. At this time she had a complete lack of luminal symptoms with faecal calprotectin $<20\mu\text{g/g}$. 12 months later, persistent purulent perianal discharge was noted and magnetic resonance imaging (MRI) scan revealed a simple perianal fistula. At colonoscopy a diagnosis of CD was confirmed and a formal EUA was performed with no seton drain required however multiple destructive fissures with large skin tags noted. She commenced infliximab induction therapy which resulted in early fistula closure (confirmed both clinically and radiologically) but continued to experience regular perianal pain during and post defecation that gradually worsened over the next 2 years.

Despite escalation of therapy to include antibiotics, co-immunosuppression with anti-TNF and dose optimized immunomodulator, opioid analgesia and psychological support, this perianal pain rapidly escalated, with complete school absence. A history suggestive of anal sphincter complex spasm was revealed due to ongoing intense pain for up to 15 minutes after defecation, only relieved with time while sitting in a warm bath. She received her first nerve stimulator-guided, four quadrant, anal intrasphincteric BT injection, resulting in immediate and complete symptom relief without complication. Over 27 months she received a total of 5 BT injections but with decreasing intervals of effectiveness after each one. Ongoing medical treatment during this time included trials of topical tacrolimus, diltiazem ointment and changes of biologic therapy both within class to dose-optimized adalimumab and out-of-class to ustekinumab. Luminal symptoms remained well controlled and there was no further evidence of fistulising disease. However, ongoing severe pain due to perianal spasm at defecation with minimal improvement following the 5th BT injection

eventually led to a diverting ileostomy 2.6 years after 1st BT injection. This resulted in marked improvement of her complicated perianal fissuring disease with no pain currently reported after a further 18 months from surgery. She continues on infliximab maintenance therapy (Table 1).

Subsequent Cases

Our second case developed severe pain during and post defecation suggestive of anal sphincter complex spasm 2 years after her CD diagnosis and while on adalimumab. Topical therapies including local anaesthetic gel and tacrolimus were ineffective and MRI scan revealed bilateral ischio-anal inflammation with posterior anal sphincter changes but no fistula. At EUA an oedematous perianal area was noted with multiple large skin tags, small fissures at 5 and 9 o'clock and a long, deep bleeding fissure at 6 o'clock disrupting the dentate line. Nerve stimulator-guided, four quadrant, anal intrasphincteric BT injection was performed, resulting in immediate symptomatic relief. Over 12 months a total of three BT injections were required during which time medical therapy was escalated to ustekinumab with steroid bridging and a change of immunomodulator to methotrexate. Each BT injection was immediately effective and without complication however perianal spasm and pain eventually returned with a significant detrimental effect on schooling and quality of life. After the third BT injection and a further change of therapy to dose optimized infliximab her symptoms did not return. Luminal disease had been well controlled with then relapse and repeat EUA and colonoscopy at 23 months from first BT injection and 14 months from third BT injection showing only mildly active colitis, healed fissures, no haemorrhoids seen but very large tags present (Table 1).

Our third case followed a similar trajectory with severe pain secondary to perianal sphincter spasm occurring 4 years after diagnosis despite early use of both infliximab and adalimumab with thiopurine co-immunosuppression and antibiotics. She received a total of 3 nerve stimulator-guided 4 quadrant anal intrasphincteric BT injections over 13 months with immediate symptom relief after each one. This patient did experience a brief episode of faecal incontinence after her first BT injection and also developed a perianal streptococcal infection, however this second complication was thought to be due to her known IgA deficiency. The last endoscopy and EUA was at 3rd BT injection and demonstrated mucosal healing with some improvement in the appearance of her deep perianal fissures; she has now had no perianal problems for a further 15 months (Table 1).

Finally by our fourth case we were able to clearly recognise symptoms suggestive of anal sphincter complex spasm early. This 5-year-old girl was referred with a suspected diagnosis of perianal CD and immediately on detailed history described symptoms of severe perianal and deep pelvic pain commencing at defecation and lasting for up to 15 minutes. She had previously presented to many different primary care doctors from 1 year of age with marked fissuring disease and skin tags which were continuously misdiagnosed as haemorrhoids and managed conservatively without follow-up. An EUA was planned together with diagnostic colonoscopy, demonstrating active rectosigmoid inflammation with granulomas, an anal canal ulcer and multiple fissures including a deep fissure extending across the dentate line at 7 o'clock. She received her first nerve stimulator-guided 4 quadrant anal intrasphincteric BT injection without complication at the time of CD diagnosis. This resulted in immediate symptom relief with ongoing clinical, biochemical and mucosal remission for 18 months on thiopurine therapy alone. Despite this early effective

management her symptoms eventually returned and topical therapies including local anaesthetic gel, zinc oxide cream and diltiazem ointment provided minimal improvement. A second BT injection was therefore required at 18 months when luminal treatment was escalated to adalimumab and she has been in clinical remission without perianal issues for a further 9 months (Table 1).

DISCUSSION

Within our patients a clear symptom complex was found to demonstrate complicated perianal fissuring, described as severe and intense perianal and deep pelvic pain with sudden onset at defecation and prolonged for up to 15 minutes. This pain cannot usually be managed with standard topical therapy or simple analgesia and has a significant effect on stooling, hygiene and patient and family quality of life. These symptoms often become the driver of increasingly intensive medical therapy, despite well controlled luminal disease, necessitating formal surgical examination under anaesthetic and revealing deep perianal fissuring disease without penetrating complications, often unable to be appreciated on simple assessment. Although uncommon, the cumulative incidence is 1.6% of all childhood and adolescent CD cases within this retrospective study of South-East Scotland.

Anorectal surgery in the presence of acute inflammation in CD should be avoided if possible. Even simple procedures may lead to faecal incontinence, poor wound healing, local sepsis and resultant social isolation of the patient^{11,16}. Perianal intrasphincteric BT injection is an ideal surgical alternative, avoiding damage to the sphincter apparatus and removing wound healing complications while providing effective symptomatic relief^{10,19}. The aim of this minimally invasive procedure is to provide a temporary chemical sphincterotomy, preventing spasm of the anal sphincter complex while allowing time for escalation of medical therapy to treat active perianal and luminal inflammation. Although BT injection is well-known, to our knowledge neurostimulation-guided BT injection is a novel therapy in fissuring perianal CD, previously only described in children with Hirschsprung disease and obstructive symptoms after pull-through surgery²⁰. Neurostimulator guided injection is likely to improve the effectiveness of this treatment by allowing more targeted delivery of

BT into the intersphincteric plane²⁰. Within our cohort 100% of patients had immediate symptomatic relief following their first injection and a single episode of faecal incontinence was reported in one patient which rapidly self-resolved.

BOX 1***Suggested management for anal sphincter spasm related to fissuring Crohn's disease***

Box 1 – Suggested management for anal sphincter spasm related to fissuring Crohn's disease*	
Initial management	Exclude perianal infection; commence stool softeners
1st line therapy	Topical local anaesthetic <i>and/or</i> topical zinc oxide cream
2nd line therapy	Topical diltiazem 2% cream <i>and/or</i> topical tacrolimus 0.1% ointment
3rd line therapy	Botulinum toxin injection <i>and</i> maximize luminal Crohn's Disease treatment (dose optimized biologic + immunomodulator)

*Assumes known lack of new fistulising perianal or pelvic disease

TABLE 1***Case characteristics***

Case	1	2	3	4
Paris phenotype at presentation	A1aB1p	A1L3L4aB1	A1L3B1	A1aL1B1p
Disease duration prior to 1 st BT injection	1.8 years	2.5 years	4.0 years	0 years
Medical therapies prior to 1 st BT injection	Thiopurine Infliximab Topical anaesthetic	Azathioprine Prednisolone Adalimumab Topical tacrolimus Topical anaesthetic	Mercaptopurine Prednisolone Infliximab Adalimumab Topical tacrolimus Topical anaesthetic	Nil
Total number of BT injections	5	3	3	2
Average duration between BT injections	6.8 months	4.6 months	6.6 months	18 months
Additional medical therapies trialled	Topical tacrolimus Topical diltiazem Adalimumab Ustekinumab	Ustekinumab Methotrexate Infliximab		Azathioprine Topical anaesthetic Topical zinc-oxide Topical diltiazem Adalimumab
Surgical management	Diverting ileostomy	Nil	Nil	Nil

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