Necrotising enterocolitis in an adult with anorexia nervosa

B Schapira¹, S Nazarian², M Thanapal², C Parmar², H Mukhtar²

¹University College London, UK

²Whittington Health NHS Trust, UK

ABSTRACT

Necrotising enterocolitis (NEC) is a rare cause of the acute abdomen in adults and carries one of the highest mortality rates in gastroenterology. However, its rarity confines research to small case reports. Both its pathogenesis and aetiology remain enigmatic in adult patients, proving timely diagnosis and management a challenge.

This paper reports on one case of NEC in an adult patient with underlying anorexia nervosa, following a seven-day period of starvation. She underwent emergency laparotomy for resection of necrotic bowel and subsequently made a good recovery.

To date, there have only been eight reports linking NEC with anorexia nervosa. We review our patient in the context of plausible mechanisms hypothesised in these cases. Successful management depends on prompt diagnosis, resuscitation and surgical intervention.

KEYWORDS

Necrotising enterocolitis – Anorexia nervosa – Total parenteral nutrition – Laparotomy – Pneumatosis intestinalis

Accepted 9 January 2020

CORRESPONDENCE TO

Benjamin Schapira, E: ben.schapira.14@ucl.ac.uk

Introduction

Necrotising enterocolitis (NEC), a causative factor in the acute abdomen, holds one of the highest mortality rates of all gastrointestinal disorders.¹ Histologically, NEC is characterised by patchy necrosis of the intestinal mucosa with gas cyst formation.² This disorder most commonly affects the terminal ileum, caecum and ascending colon, and it is often complicated by perforation, gangrene and sepsis.³ Similar clinical presentations are seen with occlusive mesenteric ischaemia, mesenteric venous thrombosis and neutropenic enterocolitis related to cardiovascular disease, thrombophilia⁴ and chemotherapy respectively.⁵ However, NEC differs through its association with non-commensal anaerobic bacterial overgrowth in the bowel wall.

While NEC is predominantly acknowledged as a neonatal gastrointestinal emergency,^{6,7} both its pathogenesis and aetiology in adult patients remain enigmatic, proving timely diagnosis and management a challenge. We report one case of NEC in a patient with anorexia nervosa admitted for nutritional support after a period of starvation. The sparsity of research into adult presentations of NEC limits the current literature to eight case reports. We therefore review the existing literature in relation to our own case, and present the comparative aetiologies and management between them.

Case history

A 22-year-old female with severe anorexia nervosa and an emotionally unstable personality disorder was admitted from an eating disorder unit for nutritional support owing to a 7-day starvation period arising from an intense fear of gaining weight. On admission to the intensive care unit, she was sedated and started on nasogastric tube feeding. She was extubated after four days, and subsequently noted abdominal pain, distension and signs of hypotensive shock. Biochemical markers highlighted a total white blood cell count of $3.0 \times 10^9/l$, C-reactive protein of 133mg/l and lactate of 5u/l. Urgent computed tomography showed extensive pneumatosis in the wall of the small bowel and duodenum, in keeping with extensive bowel infarction (Fig 1). A moderate volume of free gas in the abdominal cavity, consistent with perforation, was evident with no major vascular occlusion.

Following fluid resuscitation, the patient underwent emergency laparotomy, which proved necrotic small bowel 25cm from the duodenojejunal flexure up to 100cm from the ileocaecal junction, which was resected. A relook laparotomy was performed the next day with further resection of 40cm of dusky small bowel and formation of a double barrelled stoma. She was left with approximately 80cm of remaining small bowel. The histology report demonstrated varying degrees of ischaemia in the mucosa,

from small superficial ulcers to complete mucosal necrosis. The submucosa and muscularis externa also showed variable changes with areas of congestion, oedema and active inflammation through to necrosis with incipient perforation. Gram stains highlighted Gram negative and Gram positive organisms on the surface of the mucosa. No obvious vascular pathology was seen. *Clostridium perfringens* and vasculitic screening were reported negative. The appearance was in keeping with NEC.

Postoperatively, the patient had a high stoma output, which was managed with fluid restriction and total parenteral nutrition on the intensive care unit. She was stepped down to ward care after 8 days and transferred to the intestinal failure unit 43 days following surgery for further care of short gut syndrome and subsequently, reversal of her stoma.

Methods

The MEDLINE®, PubMed and Web of Science™ databases were searched for all journal articles on the topic of necroti(s/z)ing enterocolitis/enteritis/colitis with anorexia nervosa or eating disorders. Only case reports/series and case reports with systematic reviews were deemed eligible for review, with further eligibility criteria including human adult patients. Exclusion criteria included non-English articles, bulimia nervosa and gastric dilation/necrosis. There were no limits for dates of coverage. In total, 54 articles were identified, and screened for duplication and exclusion criteria, following which 8 full-text articles remained (Tables 1 and 2). Articles were assessed for primary measures including patient sex and age, body mass index or weight on admission, past medical history, length of refeeding prior to presentation, clinical history, investigation summary, management and outcome.

Discussion

The sparsity of research regarding NEC in adults has thwarted formulation of universal diagnostic criteria. As reviewed by Strand *et al*, the presentation of NEC is often non-specific, appearing clinically as an acute abdomen with abdominal distension, pain and shock, as in our patient.^{5,8} Other noted signs and symptoms include peritonitis,⁹ abdominal rigidity,² haematemesis and absence of bowel sounds.^{8,10} Further investigations prove characteristic appearances of the bowel. Abdominal x-ray and computed tomography often show dilated or 'fixed' bowel loops,¹¹ pneumatosis intestinalis or intramural gas revealed by bowel wall thickening,^{12–14} hepatoportal venous gas forced into circulation by increased intra-abdominal pressure and free peritoneal gas resulting from bowel wall perforation.^{9,11,14} This gas is thought to arise from mechanisms involving overgrowth and invasion of pathogenic bacteria. While most reports claim that *Clostridium perfringens* types A and C predominate in NEC,⁵ other small case studies have isolated *Klebsiella*,¹⁰ *Enterococcus* and *Pseudomonas* species.^{15,16}

Histologically, NEC presents a picture of mucosal infarction often extending to transmural necrosis.^{1,5,10} However, as in our patient, several pathology reports of samples taken during laparotomy revealed no occlusion of the mesenteric arteries supplying the portion of ischaemic bowel,^{5,9,10} suggesting an alternative mechanism to the thrombotic histology reported by Foran *et al*.¹⁷

Anorexia nervosa and necrotising enterocolitis

Anorexia nervosa is a multifaceted psychiatric disorder involving severe weight loss and malnutrition, predominantly affecting adolescent women.¹⁸ The mortality rate reaches as high as 20% at 20 years of age and is correlated with the percentage of body weight lost.² Chronic starvation has deleterious effects on all organ systems,^{18,19} especially gastrointestinal. NEC represents a rare and often fatal complication of anorexia nervosa, described only in a handful of case reports (Tables 1 and 2).

There is great variation in the mechanisms proposed as to the development of NEC in anorexia nervosa. Kaye *et al* suggest the dilation and subsequent perforation of transverse colon secondary to faecal impaction,⁹ a mechanism mirrored in the stercoral ulceration and perforation of the bowel as offered by McHugh *et al*.²⁰

Figure 1 Coronal abdominal computed tomography showing pneumatosis of the small bowel and duodenal walls with free gas in the abdominal cavity

Table 1 Review of patients, presentation and radiology in cases of necrotising enterocolitis with AN

Paper	Age (years) / sex	BMI on admission / weight loss	Presenting mental health	Diet	Length of time of refeeding	Symptoms	Radiology
Sakka, 1994 ²	20 F	50% body weight loss to 30kg	AN, depression	Not mentioned	2 days	Severe right iliac fossa pain, shock, hypothermia	AXR: no signs of note
Strand, 2017 ³	20 F	13.1kg/m ² (17.1kg/m ² 9 months earlier)	AN, depression	500kcal/day, starvation 2 days	1 month through nasogastric tube	Sudden onset pain in right abdomen, fever	CT: small and large bowel dilation with intramural gas, no obstruction; gas in ileocolic, superior mesenteric and portal veins; free fluid in abdominal cavity; caecum dilated to 9cm
Kaye, 1985 ⁹	17 F	50% weight loss over 2 years	AN	Starvation (period unknown)	2 months	Abdominal distension, pain, peritonism, vomiting, shock	AXR: free peritoneal gas with portal venous gas
Yamada, 2001 ¹⁰	41 F	29.1kg, BMI 12.2kg/m ²	AN, gout arthritis, admitted with paralytic ileus	Calorie / carbohydrate / fat restriction	No mention	Epigastric pain, vomiting, abdominal distension	AXR: signs of ileus
Diamanti, 2011 ¹²	17 F	30kg, BMI 10kg/m ²	AN, admitted with acute pancreatitis	Starvation (period unknown)	4 days enteral nutrition after 7 days total parenteral nutrition	Abdominal pain, distension, vomiting, diarrhoea, mild gastrointestinal bleeding	AXR: pneumatosis and portal venous gas
Neychev, 2015 ¹⁴	30 F	BMI 11kg/m ²	AN	Not mentioned	Not mentioned	Vomiting, diarrhoea, abdominal pain, generalised peritonitis, shock, hypothermia	AXR and CT: portal venous gas and bowel wall pneumatosis
Foran, 2016 ¹⁷	32 F	BMI reported as normal	AN (binge/purge subtype)	Carbohydrate binge/purge	No refeeding	Abdominal pain, distension and vomiting	CT: extensive pneumatosis of stomach and portal venous gas
McHugh, 2011 ²⁰	17 F	BMI 17kg/m ²	Diagnosed with partial eating disorder during admission	Not mentioned as no formal eating disorder until admission	Not mentioned	Left abdominal pain and peritonitis, absent bowel sounds	AXR: faecal loading throughout large bowel; CT: colonic perforation, free fluid and air, sigmoid dilated to 11cm

AN = anorexia nervosa; AXR = abdominal radiography; BMI = body mass index; CT = computed tomography

Paper	Time to surgery	Management	Findings at surgery	Pathology	Outcome
Sakka, 1994 ²	<24 hours	Right hemicolectomy and double barrelled colostomy; relook laparotomy for further resection	Gangrene from ileocaecal junction to splenic flexure; no arterial occlusion	Necrotising enterocolitis with positive Gram stain	Died 1 day after second relook laparotomy, which found no viable GI tract
Strand, 2017 ³	2 days	Right hemicolectomy with end ileostomy and colonic mucous fistula; no ICU; 10 days TPN, then oral feeding reintroduced	Inflamed ascending colon; circumferential necrosis near right colic flexure	Extensive gangrene with necrosis of mucosa and submucosa; no occlusion of mesenteric arteries or veins	Ileostomy reversed 7 months after surgery; discharged from eating disorder unit at 1 year
Kaye, 1985 ⁹	48 hours	Subtotal colectomy and resection of ileum with rectal mucous fistula and ileostomy	Faecal peritonitis; dilated colon with perforated transverse colon	Necrosis of rectosigmoid junction to distal third of ileum with gas bubbles in retrocolic tissues; no abnormalities of mesenteric vessels	Died 8 hours after surgery owing to septicaemia and DIC
Yamada, 2001 ¹⁰	2 days	Right hemicolectomy and end ileostomy; perioperative inotropic support	Necrotic ileum; pinhole perforation of caecum with brown, cloudy ascites	<i>Klebsiella</i> and <i>Enterococcus</i> in ascites; transmural infarction with necrosis in ileal and caecal samples; no occlusion of mesenteric arteries	Died from shock and DIC Postmortem examination: ascites, pleural effusion, GI bleed; no necrotic bowel
Diamanti, 2011 ¹²	N/A	EN stopped, TPN continued; antibiotics; gastric decompression	N/A	Stool culture: <i>Clostridium difficile</i> toxin	Intestinal pneumatosis resolved after 7 days; TPN continued for 3 weeks, then EN reintroduced; discharged at 4 months
Neychev, 2015 ¹⁴	>3 hours	Gastric decompression, antibiotics and ICU monitoring; later inotropic support and exploratory laparotomy, which found no viable GI tract	Necrosis of entire small bowel and right hemicolon	No sample resected	Died soon after surgery; no viable GI tract remaining
Foran, 2016 ¹⁷	<6 hours from presentation	Laparotomy, enterotomy and decompression; right hemicolectomy; relook laparotomy at 48 hours with further jejunal resection and end ileostomy	Small and large bowel diffusely dilated; patchy ischaemia throughout small bowel; ischaemic terminal ileum and caecum; thrombosed veins in small bowel and colonic mesentery	Ischaemic small and large bowel with variable depth necrosis; focal thrombosis in mesenteric veins	TPN for several days, then returned to EN and discharged with a plan for future stoma reversal
McHugh, 2011 ²⁰	24 hours	Laxatives started; at 24 hours, emergency laparotomy: total colectomy and end ileostomy with rectal stump sew-over	Faecal peritonitis; gross large bowel distension; sigmoid perforation	Extensive mucosal and mural inflammation around perforation	Repeat laparotomy with abdominal washout for collections and rectal stump sew-over dehiscence; full clinical recovery

Faecal impaction and constipation are among the most reported sequelae in the gastrointestinal manifestations of anorexia nervosa. However, both Yamada *et al* and Neychev and Borruso attribute NEC in their cases to microcirculation disturbance of the mesentery.^{10,14} Otherwise known as non-occlusive mesenteric ischaemia, these reports discuss the effects of chronic starvation on diminishing mesenteric blood flow, potentiating ischaemia in bowel tissue less equipped for enteral nutrition. Further support might be lent to this hypothesis in the absence of vascular thrombosis observed in necrosed samples taken during surgery. Yamada *et al* attribute low flow in their case to mesenteric vasoconstriction brought about during resuscitative inotropic support.¹⁰

While Foran *et al* describe a large binge eating session triggering their case of NEC,¹⁷ half of all cases reviewed appeared to follow the start of enteral nutrition after a prolonged period of starvation, a phenomenon also seen in our patient. Strand *et al* highlight a knock-on sequence of events linking circumstantial enteral nutrition with the onset of NEC.³ In anorexia nervosa, voluntary starvation triggers gastrointestinal stasis,^{21,22} delaying gastric emptying of both solids and liquids, slowing bowel transit time and instigating gastric or bowel dilation.^{2,10,18,23} The elevated pressures generated by such dilation diminish blood flow to regions of bowel,²⁴ resulting in ischaemia and damage to the mucosal integrity,¹² permitting invasion of pathogenic, gas forming bacteria and necrosis.¹⁶

Diamanti *et al* derive this hypothesis from infantile NEC, thought to result from mucosal ischaemia secondary to abnormal digestive motility.¹² Such events may be complemented by accumulations of pathogens enabled by slower gut transit and gut dysbiosis influenced by chronic starvation.²⁵ Sakka *et al* further exemplify the effects of anorexia nervosa on the gastrointestinal microbiome with the effects of starvation on *Clostridium difficile* B toxin survival.² Usually, the B toxin is degraded by pancreatic proteases, the passage of which is greatly reduced in the presence of gastric dilation and stasis triggered by enteral nutrition. They report this finding in the context of 'Darmbrand' disease (literally 'burnt intestine') or 'enteritis necrotans' following refeeding of prisoners of war liberated from concentration camps at the end of the Second World War.^{26,27}

In our case, it is entirely reasonable to attribute the patient's low tolerance of enteral feeding to a history of chronic starvation. Despite studies demonstrating the safety and success of enteral nutrition in treating anorexia nervosa,^{3,28} this sudden dietary overload, through mechanisms discussed, would have potentiated intestinal necrosis.

Management

Historically, NEC has proved notoriously difficult to manage. With no specific diagnostic criteria, identifying cases early is the first of many challenges. Between all cases reviewed, a proforma for management of the acute abdomen could almost be deciphered. In almost all cases, prompt fluid resuscitation with intravenous antibiotics was paramount to stabilising the patient for surgical intervention. Following

this, emergency laparotomy would enable resection of visible necrotic bowel, washout of peritonitic fluid and stoma formation. Total parenteral nutrition would follow surgery for varying lengths of time to supplement the enteral nutrition and stoma reversal would be considered.

There is much variation in the clinical response to management regimens that almost mirror each other across cases. For instance, all cases (barring Diamanti *et al*)¹² involved emergency laparotomy within 48 hours of presentation despite the difference in success. Among the eight cases reviewed, four were managed successfully until discharge and four resulted in patient death. On two occasions, laparotomy revealed an absence of any viable gastrointestinal tract, underlining the futility of resection.^{2,14} The two remaining unsuccessful cases proved NEC complicated by perforation, with death ensuing in the acute postoperative period as a result of overwhelming sepsis and disseminated intravascular coagulation.^{9,10}

These cases may shed light on the difficulty in identifying peritonitic fluid in the absence of perforation. We find similar trends in cases managed successfully with more complicated and prolonged postoperative recovery, following discoveries of perforation. Both our own case and that reported by McHugh *et al* demonstrate this complexity and the need for intensive care unit support after surgery,²⁰ an advent deemed unnecessary in all other successful cases with no mention of perforation.

Although the time between diagnosis and surgery was not of significance between successful and unsuccessful cases, there is clear benefit to the patient's location on presentation of symptoms. As seen in our own case, both Strand *et al* and Diamanti *et al* report patient presence on ward during symptom onset,^{3,12} significantly reducing the time to diagnosis and therefore time to surgery. Perhaps this would lend the most crucial determinant in the seemingly modest recovery of these cases and exemplify the value in minimising delay to surgery for a successful outcome.

In addition, it is wise to continue to hold a high suspicion for necrosis after initial resection of the ischaemic segment. Relook laparotomy was necessary both in our patient and in several others to resect further bowel and for washout of peritonitic fluid,^{17,20} the failure of which may have contributed to the death of patients in other cases.^{2,9,10}

However, despite striving for fast diagnosis, a successful surgical outcome is ultimately dependent on the patient's resilience and physiological reserve. The patient's premorbid state will engender one of the greater predictors of survival, including body mass index and deficiencies, perforation and comorbid condition.

Conclusions

NEC is a rare yet frequently fatal presentation in the adult population, which demands a high index of suspicion. Prompt diagnosis is often challenged by complex comorbidities and although the exact pathophysiology is

unclear, anorexia nervosa appears to be a recognised predisposition to NEC through disruption of bowel motility, mucosal damage and bacterial invasion. We believe that the strongest predictor of successful management is early diagnosis and intervention. Furthermore, we envisage the need for a diagnostic criterion, severity score or radiological classification system in future to improve the outcome of patients in this risk group.

References

1. Fox TP, Godavitarne C. What really causes necrotising enterocolitis? *ISRN Gastroenterol* 2012; **2012**: 628317.
2. Sakka S, Hurst P, Khawaja H. Anorexia-nervosa and necrotizing colitis - case-report and review of the literature. *Postgrad Med J* 1994; **70**: 369–370.
3. Strand M, Isaksson K, Lindelius A *et al*. Necrotizing enterocolitis in anorexia nervosa: a case report and review of the literature. *Psychosomatics* 2017; **58**: 197–202.
4. Acosta S, Ogren M, Sternby NH *et al*. Fatal nonocclusive mesenteric ischaemia: population-based incidence and risk factors. *J Intern Med* 2006; **259**: 305–313.
5. Davila ML. Neutropenic enterocolitis. *Curr Opin Gastroenterol* 2006; **22**: 44–47.
6. Lin PW, Stoll BJ. Necrotising enterocolitis. *Lancet* 2006; **368**: 1271–1283.
7. Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 590–600.
8. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns – pathogenesis, prevention and management. *Drugs* 2008; **68**: 1227–1238.
9. Kaye JC, Madden MV, Leaper DJ. Anorexia-nervosa and necrotizing colitis. *Postgrad Med J* 1985; **61**: 41–42.
10. Yamada Y, Nishimura S, Inoue T *et al*. Anorexia nervosa with ischemic necrosis of the segmental ileum and cecum. *Intern Med* 2001; **40**: 304–307.
11. Neu J, Mihatsch W. Recent developments in necrotizing enterocolitis. *J Parenter Enteral Nutr* 2012; **36(1 Suppl)**: 30S–35S.
12. Diamanti A, Basso MS, Cecchetti C *et al*. Digestive complication in severe malnourished anorexia nervosa patient: a case report of necrotizing colitis. *Int J Eat Disord* 2011; **44**: 91–93.
13. Engel RR, Virnig NL, Hunt CE, Levitt MD. Origin of mural gas in necrotizing enterocolitis. *Pediatr Res* 1973; **7**: 292.
14. Neychev V, Borruso J. Bowel ischemia and necrosis in anorexia nervosa: a case report and review of the literature. *Int J Surg Case Rep* 2015; **8C**: 141–143.
15. Gangemi A, Durgam S, Giulianotti PC. Fulminant necrotizing enteritis after revisional Roux-en-Y gastric bypass: a rare case and review of the literature. *Surg Infect Case Rep* 2017; **2**: 31–34.
16. Passaro E, Drenick E, Wilson SE. Bypass enteritis – a new complication of jejunoileal bypass for obesity. *Am J Surg* 1976; **131**: 169–174.
17. Foran AT, Clancy C, Gorey TF. Case report of the surgical management of small bowel and colonic ischaemia associated with anorexia nervosa binge/purge subtype. *Int J Surg Case Rep* 2016; **29**: 238–240.
18. Chial HJ, McAlpine DE, Camilleri M. Anorexia nervosa: manifestations and management for the gastroenterologist. *Am J Gastroenterol* 2002; **97**: 255–269.
19. Becker AE, Grinspoon SK, Klibanski A, Herzog DB. Eating disorders. *N Engl J Med* 1999; **340**: 1092–1098.
20. McHugh S, Todkari N, Moloney T, Leahy A. Stercoral perforation in a 17-year old. *Ir J Med Sci* 2011; **180**: 581–582.
21. Mehler PS, Brown C. Anorexia nervosa – medical complications. *J Eat Disord* 2015; **3**: 11.
22. Norris ML, Harrison ME, Isserlin L *et al*. Gastrointestinal complications associated with anorexia nervosa: a systematic review. *Int J Eat Disord* 2016; **49**: 216–237.
23. Holt S, Ford MJ, Grant S, Heading RC. Abnormal gastric-emptying in primary anorexia nervosa. *Br J Psychiatry* 1981; **139**: 550–552.
24. Doulberis M, Panagopoulos P, Scherz S *et al*. Update on ischemic colitis: from etiopathology to treatment including patients of intensive care unit. *Scand J Gastroenterol* 2016; **51**: 893–902.
25. Morita C, Tsuji H, Hata T *et al*. Gut dysbiosis in patients with anorexia nervosa. *PLoS One* 2015; **10**: e0145274.
26. Ma M, Li J, McClane BA. Genotypic and phenotypic characterization of *Clostridium perfringens* isolates from Darmbrand cases in post-World War II Germany. *Infect Immun* 2012; **80**: 4354–4363.
27. Zeissler J, Rassfeld-Sternberg L. Enteritis necroticans due to *Clostridium welchii* type F. *Br Med J* 1949; **1**: 267–269.
28. Zuercher JN, Cumella EJ, Woods BK *et al*. Efficacy of voluntary nasogastric tube feeding in female inpatients with anorexia nervosa. *J Parenter Enteral Nutr* 2003; **27**: 268–276.