OPEN ACCESS

Megarectum: systematic histopathological evaluation of 35 patients and new common pathways in chronic rectal dilatation

Joanne E Martin,[1,2] William English,[3,4] John V Kendall,[2] Vinayata Sheshappanavar,[2] Sara Peroos,[1] Milly West,[1] Stewart Cleeve,[5] Charles Knowles [4]

[1]Department of Cellular Pathology, Blizard Institute, Queen Mary University of London, London, UK
[2]Department of Cellular Pathology, Barts Health NHS Trust, London, UK
[3]Department of Colorectal Surgery, Barts Health NHS Trust, London, UK
[4]Department of Colorectal Surgery, Blizard Institute, Queen Mary University of London, London, UK
[5]Department of Paediatric Surgery, Barts Health NHS Trust, London, UK

Correspondence to
Professor Joanne E Martin, Department of Cellular Pathology, Blizard Institute, Queen Mary University of London, London E1 4NS, UK; j.e.martin@qmul.ac.uk

Received 13 January 2021
Revised 29 March 2021
Accepted 24 April 2021
Published Online First 25 May 2021

ABSTRACT

Aims Megarectum is well described in the surgical literature but few contemporary pathological studies have been undertaken. There is uncertainty whether 'idiopathic' megarectum is a primary neuromuscular disorder or whether chronic dilatation leads to previously reported and unreported pathological changes. We sought to answer this question.

Methods Systematic histopathological evaluation (in accord with international guidance) of 35 consecutive patients undergoing rectal excision surgery for megarectum (primary: n=24) or megarectum following surgical correction of anorectal malformation (secondary: n=11) in a UK university hospital with adult/paediatric surgical and gastrointestinal neuropathology expertise.

Results We confirmed some previously reported observations, notably hypertrophy of the muscularis propria (27 of 35, 77.1% of patients) and extensive fibrosis (30 of 35, 85.7% of patients). We also observed unique and previously unreported features including elastosis (19 of 33, 57.6%) and the presence of polyglucosan bodies (15 of 32, 46.9% of patients). In contrast to previous literature, few patients had any strong evidence of specific forms of visceral neuropathy (5 of 35, including 3 plexus duplications) or myopathy (6 of 35, including 3 muscle duplications). All major pathological findings were common to both primary and secondary forms of the disease, implying that these may be a response to chronic rectal distension rather than of primary aetiology.

Conclusions In the largest case series reported to date, we challenge the current perception of idiopathic megarectum as a primary neuromuscular disease and propose a cellular pathway model for the features present. The severe morphological changes account for some of the irreversibility of the condition and reinforce the need to prevent ongoing rectal distension when first identified.

INTRODUCTION

The term megarectum describes the radiological or operative finding of a grossly enlarged rectum often with an accompanying varying length of colonic dilatation.[1] Such dilatation is observed congenitally in short-segment Hirschsprung's disease (classic Hirschsprung's disease is associated with megacolon) and can be acquired with infection (Chagas disease) and some disorders of the endocrine or central nervous system (including spinal trauma and old age).[2] However, megarectum can also be observed in the absence of an organic cause and the term 'idiopathic' is applied.[1] Idiopathic megarectum affects both sexes roughly equally, with symptoms generally starting in early infancy or childhood.[3] A high proportion of these patients fail[4] or poorly tolerate[5] medical and behavioural[6] interventions, which do not restore rectal calibre to normal, even following several years of therapy.[7] On this basis, despite the relatively high-risk nature of surgery, resection of the enlarged rectum may be undertaken, even in childhood.[8]

Accepting the rarity of the condition, resected rectal tissue provides an opportunity for review of histopathological findings, which also might determine whether rectal dilatation in idiopathic megarectum occurs as a consequence of a primary neuromuscular disease[9–14] of the rectal wall or occurs secondary to functional changes, including behavioural or learning difficulties in which volitional stool retention may lead to chronic distension.[3 15–17] To date, pathological studies have been limited to small numbers of patients (largest study: n=24) with heterogeneous clinical presentations and a dependence on a variety of techniques, some of which are now outdated (see the Discussion section for full review of previous studies). The lack of consistency in pathological abnormalities observed to date has prevented firm conclusions regarding whether observed changes are primary or secondary. One further group of patients develop megarectum in association with rare anorectal anomalies.[18–20] Wide variations in prevalence are reported in this association (10%–50%), and the mechanism of visceral distension is not fully understood, possibly reflecting a concomitant primary neuromuscular disorder of the rectum or the effect of chronic distal stenosis before or after surgery, or both.[21]

Here we present the results of a systematic histopathological evaluation of 35 patients undergoing surgical excision of the rectum for megarectum including those considered primary 'idiopathic' and those secondary to corrected anorectal malformations. This evaluation is in keeping with international guidance on techniques and reporting of gastrointestinal (GI) neuromuscular pathology.[22]

METHODS

Patients

Consecutive surgical resection specimens from patients with medically intractable megarectum

To cite: Martin JE, English W, Kendall JV, *et al*. *J Clin Pathol* 2022;**75**:651–657.

Table 1 Clinical data of 35 patients with megarectum

Sex	20 male	15 female (ratio 1.3:1)
Main diagnosis	Idiopathic megarectum	24 (68.6%)
	Anorectal malformation and megarectum	11* (31.4%)
Age at diagnosis	Median age at diagnosis	8 years (range 2–25 years)
Other diagnoses	Psychobehavioural diagnosis	7† (20.0%)
	Developmental delay, premature birth, epilepsy, diabetes, hypermobility syndrome	Each category has 2 or fewer
Diagnostic imaging	Number of patients with available imaging for review‡	20 (57.1%)
	Median rectal diameter on imaging	8.5 cm (range 5.3–19.0 cm)
Anorectal physiology	Number of patients with Anorectal physiology results for review	15
Operative details	Median age at operation	13 years (range 2–48 years)
	Anterior resection§	26 (74.3%)
	Vertical reduction rectoplasty	7 (20.0%)
	Anterograde continence enema surgery	4 (11.4%)

*Includes patients with sacrococcygeal teratoma (Currarino triad), VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalitie) and Turner's syndrome (2 or fewer each).
†Includes Asperger's syndrome.
‡Includes 18 plain radiographs, 8 defaecating proctograms, 2 CT and 1 MRI scan.
§Includes 7 patients with extended resections including sigmoid or left hemicolon; defunctioning loop ileostomy used as routine (some patients had stoma prior to surgery).

treated surgically were collated from the files of the Royal London Hospital Cellular Pathology Department (part of Barts Health NHS Trust) over a period of 30 years (1990–2019) using a text-based search of the laboratory database. Patients were only excluded if no slides were available in the files for review, as for example where slides for second opinion had been returned to the original laboratory. Both secondary and idiopathic megarectum samples were studied; a clinical summary of patients is shown in table 1.

Histopathology

Techniques for histopathological evaluation followed the London classification recommendations,[22] but with the addition of the MTOCH1 stain, a COX1 antigen-related immunohistochemical method which highlights the neuronal cell bodies of all classes. Elastic van Gieson (EVG) staining is of particular importance since haematoxylin van Gieson methods do not demonstrate elastin. The full panel of tinctorial and immunohistochemical stains used is shown in table 2. Hypoganglionosis was assessed based on gross loss of ganglion cells rather than neuronal counting. This is commensurate with international technical guidance[22] which acknowledges the difficulty of classifying subtle reductions in neuronal number.

RESULTS

Findings in the whole cohort

Histopathological examination of rectal tissue from all 35 patients showed a range of findings (table 3 and figure 1). The most common finding was the presence of extensive fibrosis (30 of 35 patients), with the submucosa most affected (27 of 35 patients). Fibrosis was also evident in the region around the myenteric ganglia and in the muscularis propria in about half of patients with fibrosis. This fibrosis stained red with the EVG method indicating collagen and varied from fine fibrils to thick bands of collagen. The next most common finding was hypertrophy of the muscularis propria (27 of 35 patients), usually involving both muscle layers and always involving the circular muscle layer. In some cases, gross hypertrophy was evident. Where hypertrophy was present, intramuscular fibrosis was also often present.

EVG staining revealed evidence of elastin deposition in over half of patients (19 of 33 patients). This elastosis was profound in several patients, where it was present in all or nearly all major layers of the rectal wall, and in others it was more focal but with a variable distribution. Elastosis was often accompanied by a degree of fibrosis, but the latter was not always prominent. In some patients the elastin was associated with a granulomatous

Table 2 Histological techniques used in the assessment of rectal tissue

Technique	Target and brief utility
Tinctorial stains	
H&E on multiple blocks/levels	General structure
Elastic van Gieson	Connective tissue (collagen, elastin)
Congo red	Amyloid
Periodic acid-Schiff±diastase	Carbohydrates and mucins
Immunostains	
MTOCH1*	Identification and quantification of neurons and cell morphology (diagnosis of aganglionosis, hypoganglionosis and hyperganglionosis)
c-Kit (CD117)	Interstitial cells of Cajal, mast cells
CD45/CD3	White cells/T lymphocytes: to clarify nature of inflammatory infiltrates in ganglionitis or leiomyositis
Alpha smooth muscle actin and desmin	Confirm myocyte loss in myopathies; specific deficiency may also accompany some forms of gastrointestinal neuromuscular diseases

*Alternative to the London classification,[21] which recommends NSE, PGP9.5 or Hu C/D.

Table 3 Pathological findings on examination of full-thickness rectal tissue from all patients with megarectum

Finding	n (%)	Notes
Melanosis	0/33 (0)	
Fibrosis	30/35 (85.7)	Focal submucosal only: 8 Submucosal and periplexus: 4 Submucosal and muscularis propria: 2 Submucosal, periplexus and muscularis propria: 10 Other combinations: 6
Elastosis	19/33 (57.6) 1 site: 8 2 sites: 6 3 sites: 5	Submucosal only: 1* Periplexus only: 2 Muscularis propria only: 4† Serosa only: 1 Submucosa and muscularis propria: 2 Submucosa and periplexus: 1 Periplexus and muscularis propria: 1‡ Periplexus and serosa: 1 Muscularis propria and serosa: 1 Muscularis mucosae, submucosa and muscularis propria: 1 Submucosa, periplexus and muscularis propria: 2 Submucosa, muscularis propria and serosa: 2
Neuronal abnormalities	6/35 (17.1)	Degenerative or inflammatory neuropathy: 0 Hypoganglionosis: 2 Duplicated plexus: 3 Single ectopic ganglion: 1
Muscular abnormalities	Abnormal muscle layers: 14/35 (40.0)	Degenerative or inflammatory myopathy: 0 Submucosal metaplasia: 8 Duplication of circular muscle layer: 3 Partial duplication longitudinal muscle layer: 2 Grossly thinned: 1§
	Muscle hypertrophy: 27/35 (77.1)	Hypertrophy circular muscle layer only: 2 Hypertrophy both muscle layers: 25
Decreased interstitial cells of Cajal	6/27 (22.2)	Qualitative assessment: only gross reductions reported
Polyglucosan bodies	15/32 (46.9)	Present on single section: 6 Present on multiple sections: 9

*Predominantly around the submucosal vessels.
†Includes one patient with elastosis confined to partial extra muscle layer.
‡With granulomatous response to elastin fibres.
§Appearances suggest developmental abnormality.

response, including focally in the mid part of the muscularis propria in one case. In this latter situation the elastin fibres appeared fragmented and coarse only in the area of inflammation (see figure 1M,N), not elsewhere. In the control group, and in those without significant elastin deposition, elastin fibres were seen in the expected distribution in the blood vessel walls, in a fine mesh in the muscularis mucosa and the luminal most aspect of the muscularis propria. Elastin is also normally present in a fine line around the myenteric plexus and in between the muscle fascicula of the muscularis propria (figure 2).

Polyglucosan bodies, demonstrated on periodic acid-Schiff staining, were evident in the muscularis propria in 15 of 32 patients. Since these can be a patchy finding, multiple sections were examined, demonstrating that in 9 of those 15 patients with polyglucosan bodies these were present in more than one, and sometimes several sections.

Classically described abnormalities of nerve and muscle (enteric neuropathies and myopathies) were rare or absent. Only two patients had evidence of hypoganglionosis and none had a classic degenerative myopathy with or without vacuolation (even by a-smooth muscle actin and desmin immunostaining). In contrast, several patients had evidence of gross morphological changes in the organisation of the nerve plexus and/or muscle. Thus three patients had duplication of the myenteric plexus and three had complete duplication of the circular muscle layer. Eight patients showed smooth muscle metaplasia of the submucosa, often in association with fibrosis or elastosis or both. Reductions in numbers of interstitial cells of Cajal were noted in only 6 of 27 patients. No evidence of amyloid deposition was detected using Congo red staining.

Findings by main groups

The above findings were common to both groups of patients studied (table 4). Thus, while there were some slight variations in the proportion of patients with each histological finding, there were no major differences, with the exception that duplications of nerve and muscle were confined to the secondary (anorectal malformation) group, perhaps reflecting a parallel developmental abnormality (in addition to evident anorectal malformation).

DISCUSSION

Even taking all causes together, megarectum is acknowledged as a rare cause of severe intractable constipation in children and adults.[1 3 6 15] The category generally excludes specific causes such as Hirschsprung's disease, where the dilatation is consequent on mechanical obstruction caused by the distal narrowed aganglionic segment.

Several case series and case reports on megarectum have described variable changes of all three main final effectors of sensorimotor function (enteric nervous system, smooth muscle and interstitial cells of Cajal).[9–14 23] Several report smooth muscle hypertrophy[9–11] with or without some degree of fibrosis or connective tissue abnormality.[24] Some have also reported changes in neuronal staining,[9 10 14] while others have found no abnormality.[13 25] Overall, reported changes have been inconsistent. Further, these studies have generally included only relatively small numbers of rectal tissues from patients with defined idiopathic megarectum (most being mixed series of patients with megacolon and megarectum[24]) and all predate the development of international guidance on techniques and reporting of GI neuromuscular pathology.[22] As part of a centralised pathological review of patients with GI neuromuscular disease, we re-evaluated all rectal tissues obtained from patients with idiopathic megarectum with techniques in keeping with this guidance.

The opportunity afforded by our large paediatric surgery practice, in addition to our specialist practice, both surgical and histopathological, in adult GI dysmotility, allowed us to use 'primary', that is, idiopathic megarectum, and 'secondary' megarectum groups and compare findings for commonalities and differences to gain some insight into the mechanistic

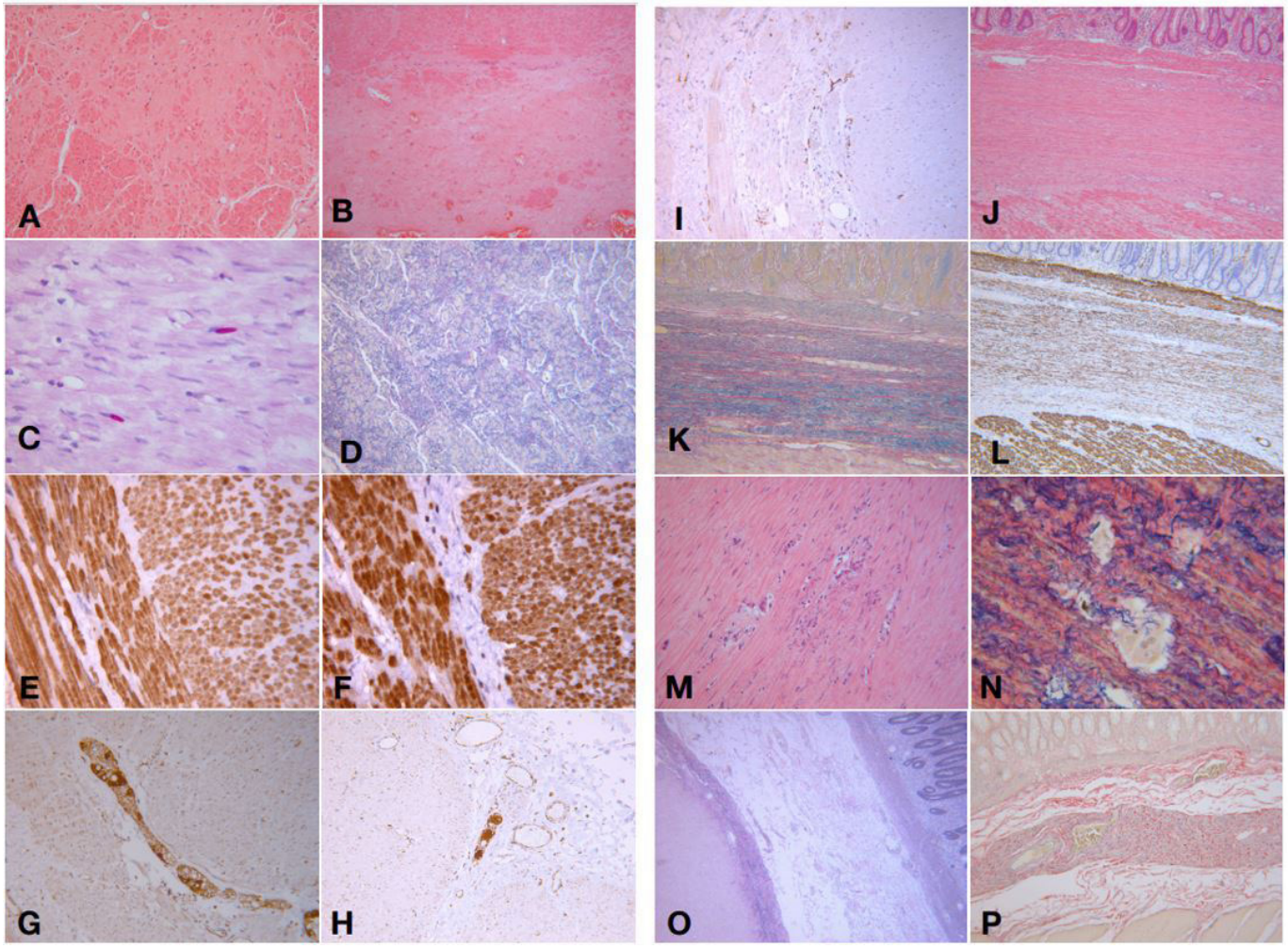

Figure 1 Extensive replacement of the muscularis propria by apparent 'fibrosis' (A,B), and in some areas leading to the appearance of a 'lost layer' of longitudinal smooth muscle (B) (H&E ×25). (C) Ovoid polyglucosan bodies (purple) within the smooth muscle fibres of the muscularis propria (periodic acid-Schiff stain ×40). (D) Areas of apparent 'fibrosis' showing extensive elastosis (stained black) (elastic van Gieson ×25). (E,F) Normal pattern of smooth muscle actin (E) and desmin (F) immunostaining in preserved areas of the smooth muscle of the muscularis propria (x40). (G,H) Normal ganglia of the myenteric (G) and submucosal (F) plexus stained with the MTOCH1 antibody, highlighting ganglion cell bodies (x25). (I) Normal pattern of CD117 immunostaining highlighting interstitial cells of Cajal (x40). (J,K,L) Submucosal smooth muscle metaplasia and fibroelastosis filling the submucosa between the muscularis mucosa and the muscularis propria: H&E section (×25) (J), elastic van Gieson (K) and desmin (L) immunostaining. (M,N) Intramuscular area of abnormal elastin fibres within the hypertrophic circular layer of the muscularis propria: H&E (×25) (M), including a multinucleate giant cell reaction. Elastic van Gieson stain (×40) showing a large multinucleate giant cell (light brown colour) and surrounding coarse elastin fibres (N). (O,P) Defined bands of elastosis within the submucosa, one deep and adjacent to the muscularis propria (O) and the other in the midpoint of the submucosa (P) (elastic van Gieson ×25).

processes. In our series we show some similarities but also some major differences in findings to those seen in the classic study of Gattuso *et al*.[10] Our series is larger and includes both idiopathic and secondary megarectum. Hypertrophy of smooth muscle, despite the presence of dilatation, was a common feature of both series, as was fibrosis; however, our series included 85.7% of cases with fibrosis, a higher rate than Gattuso *et al*,[9] and a great deal of elastosis, a feature not commented on in previous studies. We used an EVG preparation in our series, which is a sensitive detector of both collagen and elastin.[26] Previous studies have not employed this method, which may explain the lack of previous reporting. It is very easy to confuse elastosis with fibrosis on an H&E preparation (figure 1). Similarly, we report polyglucosan bodies as a common feature of both idiopathic and secondary megarectum. The bodies are easy to miss on a section if you are unaccustomed to recognising them, and the majority of laboratories receiving specimens relating to GI dysmotility do not perform the full range of recommended stains and may well be unfamiliar with identification of inclusion bodies.[27 28]

The common patterns of pathology seen in both idiopathic and secondary megarectum groups suggest that hypertrophy, fibrosis, elastosis and polyglucosan body formation are common features of rectal dilatation rather than primary causal pathology. While little primary research has been performed on GI smooth muscle, inferences may be drawn from a range of other studies on smooth muscle. Using a wide range of such literature, hypertrophy, fibrosis, elastosis and indeed the formation of polyglucosan bodies seen in the patients reported here may be linked through secondary mechanisms, as depicted in a summary form in figure 3. Stress from stretching is known to cause smooth muscle hypertrophy in airway smooth muscle via inhibition of glycogen synthase kinase 3 beta (GSK3B).[29] GSK3B inhibition

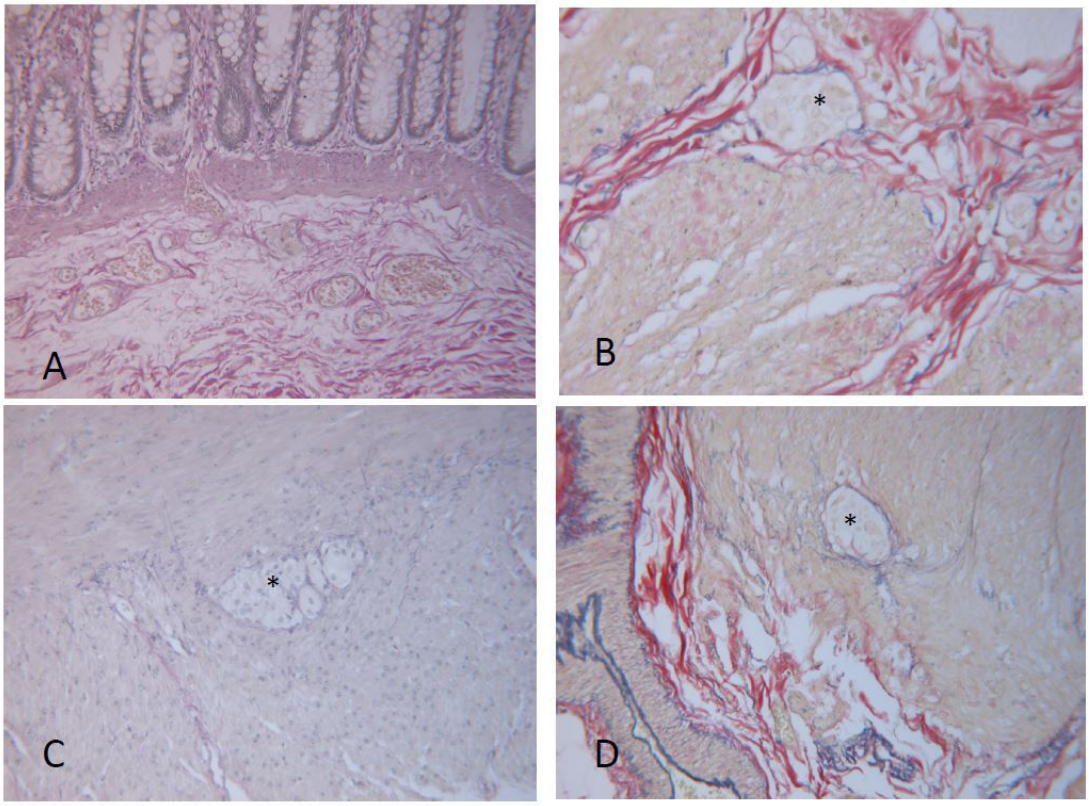

Figure 2 Normal distribution of elastin in the rectum with elastic van Gieson staining. (A) Mucosa and muscularis mucosa. (B) Submucosa/muscularis propria interface; the asterisk marks the submucosal ganglion. (C) Myenteric plexus at the interface of the circular and longitudinal muscle layers; the asterisk marks the myenteric ganglion. (D) Myenteric plexus (asterisk) and longitudinal muscularis propria junction with serosa.

has also been reported to play a critical role in hypertrophy of cardiac myocytes[30] and in human cardiac muscle, leading to increased beta-catenin expression and subsequent protein expression increase and hypertrophy.[31]

GSK3B is a key enzyme in a range of intracellular processes, not just hypertrophy. GSK3B is normally activated and is the main regulator of glycogen synthase (GS). When GSK3B is inhibited there is an increase in the activity of GS kinase.[32 33] A balance of GS and glycogen branching enzyme (GBE) is key to the formation of soluble glycogen. Insoluble deposits of non-branching polyglucosan can be deposited when this balance is disrupted by either a deficiency of GBE or an increase in GS.[34 35] It is conceivable that the smooth muscle hypertrophy seen in megarectum is accompanied by an increase in the activity of GS, which might overwhelm the normal balance of glycogen production and predispose to polyglucosan body formation.

When subjected to laminar shear stress vascular smooth muscle cells will deposit tropoelastin in vitro in two-dimensional settings,[36] but the recent demonstration of the production of mature elastin fibres and elastogenesis-related proteins by smooth muscle cells in a three-dimensional matrix[37] shows that shear stress may produce a functional change in smooth muscle cells that can create the setting for elastogenesis. We have already shown that smooth muscle cells in visceral myopathy may transform into myofibroblastic phenotypes and be associated with the production of collagen,[38] and in megarectum it seems highly likely that the same process may be occurring in response to smooth muscle injury. Thus, the stretch and lateral shear produced by rectal dilatation can create conditions that result in smooth muscle hypertrophy, fibrosis, elastogenesis and polyglucosan body formation in keeping with our findings. The commonality of these features in both idiopathic and secondary

Table 4 Main histological findings by disease group

Finding	Total, n (%)	Idiopathic megarectum, n (%)	Post-ARM megarectum, n (%)
Fibrosis	30/35 (85.7)	19/24 (79.1)	11/11 (100)
Elastosis	19/35 (54.3)	14/24 (58.3)	5/11 (45.4)
Neuronal abnormalities	6/35 (17.1)	2/24 (8.3)	4/11 (36.4), including all 3 plexus duplications
Muscular abnormalities	Abnormal muscle layers: 14/35 (40)	9/24 (37.5)	5/11 (45.4), including all 3 circular muscle duplications
	Muscle hypertrophy: 27/35 (77.1)	16/24 (66.7)	10/11 (90.9)
Decreased interstitial cells of Cajal	6/27 (22.2)	5/20 (25)	1/7 (14.2)
Polyglucosan bodies	15/32 (46.8)	11/22 (50)	4/10 (40)

ARM, anorectal malformation.

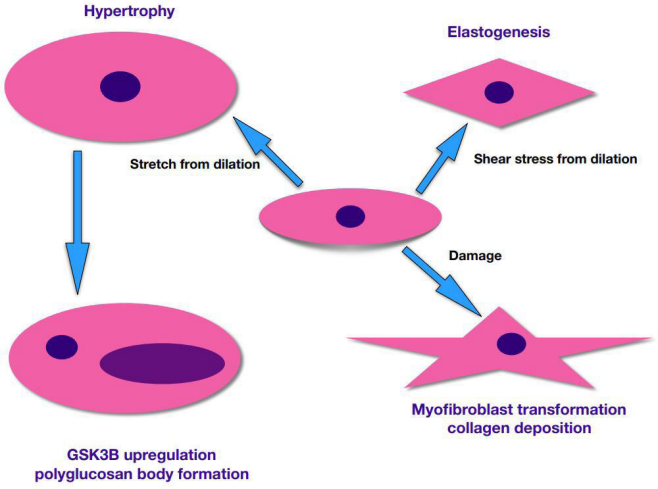

Figure 3 Proposed model of smooth muscle changes in the megarectum. GSK3B, glycogen synthase kinase 3 beta.

megarectum provides evidence of these processes as a final common pathway in chronic rectal dilatation.

We acknowledge limitations to the study, which include the small number of overall patients and the general descriptive nature of the methodology. However we note the rarity of the condition (St Mark's Hospital, London identified only 92 genuine cases in a 27-year period[3]), making our pathological series the largest published to date. Significantly, the current study adds to a literature devoid of contemporary pathology reporting for this condition. While acknowledging that the above discussion on mechanism is hypothetical, our findings mirror two important clinical observations. First, profound structural changes such as high degrees of fibrosis may account for the irreversibility of gross megarectum necessitating recourse to major surgery,[8] and second that earlier stages of the disease, for example, when first recognised, justify the current clinical approach of emptying the rectum (sometimes by manual disimpaction) and thence keeping it empty[3] by means such as rectal and oral laxatives, and antero-grade and retrograde irrigation.

Take home messages

- ⇒ Megarectum is a rare and severe condition with poorly understood pathophysiology, and few significant studies over the last 20 years.
- ⇒ In the largest case series reported to date, we have identified characteristic features of the pathology of megarectum not previously reported, including the presence of elastosis and polyglucosan bodies.
- ⇒ The presence of similar features in both primary and secondary megarectum cohorts is highly suggestive of a common, and secondary, cellular process that is potentially preventable and we propose a mechanism for this.

Handling editor Runjan Chetty.

Acknowledgements We thank Mr Harry Ward and Mr Chris Chan, Consultant Surgeons, Barts Health NHS Trust, for their support.

Contributors JEM and CK conceived the study and analysed the data. JEM conceived the experimental methods. JVK, VS, SP and MW carried out the experiments. SC and WE obtained and synthesised clinical patient data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Funding The group appreciates funding support from UK Charity: Pseudo-Obstruction Research Trust in our wider work on neuromuscular disease of the bowel. The work of JVK was supported by a bursary from the Isaac Shapera Trust.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was part of the Barts Health NHS Trust registered clinical effectiveness programme number 10728 and was exempt from full ethical committee review.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD
Charles Knowles http://orcid.org/0000-0001-9854-6754

REFERENCES

1 Todd IP. Discussion on megacolon and megarectum with the emphasis on conditions other than Hirschsprung's disease. *Proc R Soc Med* 1961;54:1035–40.
2 Ehrenpreis T. Megacolon and megarectum in older children and young adults. classification and terminology. *Proc R Soc Med* 1967;60:799–801.
3 Gattuso JM, Kamm MA. Clinical features of idiopathic megarectum and idiopathic megacolon. *Gut* 1997;41:93–9.
4 Lane RH, Todd IP. Idiopathic megacolon: a review of 42 cases. *Br J Surg* 1977;64:305–10.
5 Kamm MA, Stabile G. Management of idiopathic megarectum and megacolon. *Br J Surg* 1991;78:899–900.
6 Mimura T, Nicholls T, Storrie JB, *et al*. Treatment of constipation in adults associated with idiopathic megarectum by behavioural retraining including biofeedback. *Colorectal Dis* 2002;4:477–82.
7 Goligher JC. Discussion on megacolon and megarectum with the emphasis on conditions other than Hirschsprung's disease. *Proc R Soc Med* 1961;54:1053–5.
8 Gladman MA, Scott SM, Lunniss PJ, *et al*. Systematic review of surgical options for idiopathic megarectum and megacolon. *Ann Surg* 2005;241:562–74.
9 Gattuso JM, Hoyle CH, Milner P, *et al*. Enteric innervation in idiopathic megarectum and megacolon. *Int J Colorectal Dis* 1996;11:264–71.
10 Gattuso JM, Kamm MA, Talbot JC. Pathology of idiopathic megarectum and megacolon. *Gut* 1997;41:252–7.
11 Gattuso JM, Smith VV, Kamm MA. Altered contractile proteins and neural innervation in idiopathic megarectum and megacolon. *Histopathology* 1998;33:34–8.
12 Stabile G, Kamm MA. Surgery for idiopathic megarectum and megacolon. *Int J Colorectal Dis* 1991;6:171–4.
13 Belliveau P, Goldberg SM, Rothenberger DA, *et al*. Idiopathic acquired megacolon: the value of subtotal colectomy. *Dis Colon Rectum* 1982;25:118–21.
14 Meier-Ruge WA, Müller-Lobeck H, Stoss F, *et al*. The pathogenesis of idiopathic megacolon. *Eur J Gastroenterol Hepatol* 2006;18:1209–15.
15 Athanasakos EP, Kemal KI, Malliwal RS, *et al*. Clinical and psychosocial functioning in adolescents and young adults with anorectal malformations and chronic idiopathic constipation. *Br J Surg* 2013;100:832–9.
16 Afzal N, Murch S, Thirrupathy K, *et al*. Constipation with acquired megarectum in children with autism. *Pediatrics* 2003;112:939–42.
17 Pinkerton P. Psychogenic megacolon in children: the implications of bowel negativism. *Arch Dis Child* 1958;33:371–80.
18 Paris J, Christiaens L. Megarectum par stenose congenitale de l'anus associee a une agenesie partielle du sacrum. *Pediatrie* 1957;12:458–60.
19 Schmidt D, Jenetzky E, Zwink N, *et al*. Postoperative complications in adults with anorectal malformation: a need for transition. German network for congenital Uro-REctal malformations (CURE-Net). *Pediatr Surg Int* 2012;28:793–5.
20 Borg H, Holmdahl G, Doroszkievicz M, *et al*. Longitudinal study of lower urinary tract function in children with anorectal malformation. *Eur J Pediatr Surg* 2014;24:492–9.
21 Xiao H, Huang R, Cui DX, *et al*. Histopathologic and immunohistochemical findings in congenital anorectal malformations. *Medicine* 2018;97:e11675.
22 Knowles CH, De Giorgio R, Kapur RP, *et al*. Gastrointestinal neuromuscular pathology: guidelines for histological techniques and reporting on behalf of the gastro 2009 international Working group. *Acta Neuropathol* 2009;118:271–301.
23 Stabile G, Kamm MA, Phillips RK, *et al*. Partial colectomy and coloanal anastomosis for idiopathic megarectum and megacolon. *Dis Colon Rectum* 1992;35:158–62.
24 Wedel T, Spiegler J, Soellner S, *et al*. Enteric nerves and interstitial cells of Cajal are altered in patients with slow-transit constipation and megacolon. *Gastroenterology* 2002;123:1459–67.

25 Stabile G, Kamm MA, Hawley PR, *et al*. Colectomy for idiopathic megarectum and megacolon. *Gut* 1991;32:1538–40.
26 Kazlouskaya V, Malhotra S, Lambe J, *et al*. The utility of elastic Verhoeff-Van Gieson staining in dermatopathology. *J Cutan Pathol* 2013;40:211–25.
27 Knowles CH, Nickols CD, Feakins R, *et al*. A systematic analysis of polyglucosan bodies in the human gastrointestinal tract in health and disease. *Acta Neuropathol* 2003;105:410–3.
28 Martin JE, Hester TW, Aslam H, *et al*. Discordant practice and limited histopathological assessment in gastrointestinal neuromuscular disease. *Gut* 2009;58:1703–5.
29 Mohamed JS, Lopez MA, Boriek AM. Mechanical stretch up-regulates microRNA-26a and induces human airway smooth muscle hypertrophy by suppressing glycogen synthase kinase-3β. *J Biol Chem* 2010;285:29336–47.
30 Haq S, Choukroun G, Kang ZB, *et al*. Glycogen synthase kinase-3beta is a negative regulator of cardiomyocyte hypertrophy. *J Cell Biol* 2000;151:117–30.
31 Rezvani M, Liew CC. Role of the adenomatous polyposis coli gene product in human cardiac development and disease. *J Biol Chem* 2000;275:18470–5.
32 Lohi H, Ianzano L, Zhao X-C, *et al*. Novel glycogen synthase kinase 3 and ubiquitination pathways in progressive myoclonus epilepsy. *Hum Mol Genet* 2005;14:2727–36.
33 Oreña SJ, Torchia AJ, Garofalo RS. Inhibition of glycogen-synthase kinase 3 stimulates glycogen synthase and glucose transport by distinct mechanisms in 3T3-L1 adipocytes. *J Biol Chem* 2000;275:15765–72.
34 Moses SW, Parvari R. The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies. *Curr Mol Med* 2002;2:177–88.
35 Kakhlon O, Glickstein H, Feinstein N, *et al*. Polyglucosan neurotoxicity caused by glycogen branching enzyme deficiency can be reversed by inhibition of glycogen synthase. *J Neurochem* 2013;127:101–13.
36 Noda K, Dabovic B, Takagi K, *et al*. Latent TGF-β binding protein 4 promotes elastic fiber assembly by interacting with fibulin-5. *Proc Natl Acad Sci U S A* 2013;110:2852–7.
37 Hinderer S, Shena N, Ringuette L-J, *et al*. In vitro elastogenesis: instructing human vascular smooth muscle cells to generate an elastic fiber-containing extracellular matrix scaffold. *Biomed Mater* 2015;10:034102.
38 Martin JE, Benson M, Swash M, *et al*. Myofibroblasts in hollow visceral myopathy: the origin of gastrointestinal fibrosis? *Gut* 1993;34:999–1001.