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

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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 ano rectal 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 reversibility 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 fail4 or poorly tolerate5 medical and behavioural6 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 disease9-14 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.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 ano rectal 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 ano rectal 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...
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, 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 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

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**Table 1** Clinical data of 35 patients with megarectum

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

*Includes patients with sacrococcygeal teratoma (Currarino triad), VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormality) 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).

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**Table 2** Histological techniques used in the assessment of rectal tissue

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

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

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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. 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). Several report smooth muscle hypertrophy with or without some degree of fibrosis or connective tissue abnormality. 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) and all predate the development of international guidance on techniques and reporting of GI neuromuscular pathology. 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 processes. In our series we show some similarities but also some major differences in findings to those seen in the classic study of...
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., 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. 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.

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). GSK3B inhibition...
has also been reported to play a critical role in hypertrophy of cardiac myocytes and in human cardiac muscle, leading to increased beta-catenin expression and subsequent protein expression increase and hypertrophy. 

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. 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. 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.

Table 4  Main histological findings by disease group

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

ARM, anorectal malformation.
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), 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, 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 by means such as rectal and oral laxatives, and anterograde and retrograde irrigation.

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

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.

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