Hyperganglionosis mimicking Hirschsprung's disease

Anna C Athow, M Isabel Filipe, D P Drake

Abstract

Three patients with hyperganglionosis are reported in whom an initial diagnosis of Hirschsprung's disease was suspected. In one patient there was a classic presentation with constipation, in another Hirschsprung's disease coexisted, and in the third the initial inadequate suction rectal biopsy specimen was suggestive of Hirschsprung's disease on acetylcholinesterase staining. Evidence of hypertrophy and hyperplasia of the intermuscular and submucosal plexuses on a full thickness bowel biopsy specimen was used to confirm the diagnosis of hyperganglionosis, suggested by the characteristic demonstration of moderate increase in the number of acetylcholinesterase stained nerve fibres in the lamina propria mucosae on rectal biopsy. Surgical management was guided by clinical signs. Two patients had colonic resections; the third had temporary stomal diversion.

Hyperganglionosis is rarer than Hirschsprung's disease but is known to mimic it. We suggest full thickness bowel specimens are needed to confirm the diagnosis and that inadequate rectal suction biopsies must be interpreted with caution.

In 1970 a description of 'les megacolons avec hyperplasie des plexus myenteriques' was given by Nezelof *et al.*¹ They reported three paediatric patients with severe constipation in whom there was remarkable hypertrophy and hyperplasia of the submucosal and intermuscular ganglion plexuses on histology of rectal biopsy specimens. Two of the children had no extra-intestinal abnormality but the third developed a medullary carcinoma of the thyroid. From a review of the literature they noted that similar histological changes in the bowel had been reported, affecting the bowel alone, or in association with various endocrine tumours. There have been other more recent French case reports.²⁻⁴

In 1971 Meier-Ruge presented three further patients with a similar clinical condition.⁵ He stained rectal biopsy specimens for acetylcholinesterase and found there was increased activity of the parasympathetic nerve fibres in the lamina propria mucosae. There was also the occasional presence of isolated ganglion cells or smooth muscle in the lamina propria mucosae, in addition to hyperplasia and hypertrophy of the submucosal and intermuscular ganglion plexuses. He named the condition 'neuronal colonic dysplasia', which was taken up in other case reports.⁶⁻¹⁰

Subsequent authors working in collaboration with Meier-Ruge in Switzerland, Germany, and Chile,¹¹⁻¹³ and Munakata *et al* in Japan^{14 15} have called the condition 'neuronal intestinal dysplasia' and have reported larger series of cases occurring both alone and in association with Hirschsprung's disease. Garrett *et al* considered 'hyperganglionosis' a more accurate name for the condition as 'dysplasia' embraces all abnormalities of innervation of the bowel including Hirschsprung's disease.^{16 17}

Patients and methods

Between January 1984 and December 1987, 84 children were investigated for constipation or bowel obstruction with rectal biopsy (52 suction and 32 full thickness). Seventy one of these 84 biopsy specimens (84.5%) were stained for acetylcholinesterase by the method of Lake *et al.*¹⁸ The other 13 specimens (15.5%) were fixed, embedded in paraffin, and stained with haematoxylin and eosin.

The features looked for to make a diagnosis of hyperganglionosis were those of Meier-Ruge.^{11 19} (1) Hyperplasia of the submucosal and intermuscular plexuses with formation of giant ganglia. (2) Moderate rise in acetylcholinesterase activity in parasympathetic nerve fibres of the lamina propria mucosae and circular muscle, acetylcholinesterase activity being not as greatly raised as in Hirschsprung's disease. (3) The presence, sometimes, of isolated ganglion cells in the lamina propria mucosae and between the muscle layers of the muscularis mucosae. In addition we looked for the presence of thick nerve fibres in the submucosa, muscularis propria, and serosa.^{1 17}

We did not have the facilities to stain for adrenergic innervation and therefore could not look for the other feature mentioned by Meier-Ruge: hypoplasia or aplasia of the sympathetic innervation of the myenteric plexus. This feature however has not been confirmed by Garrett and Howard.¹⁶

Results

There were three patients with hyperganglionosis that was proved on a full thickness biopsy specimen, one of whom had coexisting Hirschsprung's disease. There were a further 14 patients with Hirschsprung's disease.

CASE HISTORIES

Patient 1

This patient was a twin whose mother was

United Medical
and Dental Schools of
Guy's and St Thomas's
Hospitals,
London,
Department of
Paediatric Surgery
Anna C Athow
D P Drake

Department of
Histopathology
M Isabel Filipe

Correspondence to:
Mr D P Drake, The Hospital
for Sick Children,
Great Ormond Street,
London WC1N 3JH.

Accepted 14 July 1991

Figure 1 Patient 1. Large bowel wall submucosa showing increased numbers of thick tortuous nerve trunks and hyperplasia of ganglion cells. (Haematoxylin-eosin stain $\times 350$.)

Figure 2 Patient 2. Large bowel wall. The submucosa contains numerous clusters of ganglion cells, some of which are very large. The occasional ganglion cell is seen in the lamina propria (arrow). (S-100 protein by immunoperoxidase method $\times 175$.)

Figure 3 Patient 2. Large bowel wall showing hyperplasia of the nerve fibres in the intermuscular plexus. (Haematoxylin-eosin stain $\times 175$.)

diabetic. He presented on the third day of life with bile stained vomiting, abdominal distension, and delay in passing meconium. A plain radiograph of the abdomen showed bowel obstruction confirmed at laparotomy. A congested segment of ileum containing a milk plug was resected and a split ileostomy fashioned. Hirschsprung's disease was queried on the suction rectal biopsy specimen at 13 days but a repeat specimen one month later was suggestive of hyperganglionosis due to the prominent clumps of ganglion cells. At 4.5 months the ileum was reanastomosed and a sigmoid colostomy fashioned. The histology of the appendix revealed a striking appearance of a hyperplastic intermuscular plexus with many immature ganglion cells and thick nerve fibres breaking up the circular muscle. After a further four months the sigmoid colostomy was closed. The histology of the colon was similar (fig 1). The patient has continued to thrive and he has a normal bowel habit. His twin developed normally.

Patient 2

Aged 5.5 months this patient presented with severe constipation, a distended abdomen, and failure to thrive. The histology of a full thickness rectal biopsy specimen was suggestive of hyperganglionosis. A barium enema showed massive faecal loading of the colon. The diagnosis of hyperganglionosis was confirmed on repeat full thickness rectal biopsy. At 8 months of age a right transverse colostomy was carried out with removal of the appendix and Meckel's diverticulum, and full thickness biopsies of the transverse and sigmoid colon were taken. All showed hypertrophy and hyperplasia of the submucosal (fig 2) and intermuscular plexuses (fig 3). A barium distal loopogram revealed irregularity of the rectum and descending colon with residual barium at 24 hours. A total colectomy and ileorectal anastomosis was performed at 14 months. Histochemistry of the descending colon showed hyperganglionosis whereas the ascending colon was spared. He has gained weight satisfactorily and has regular bowel actions two or three times a day.

Patient 3

This 3 year old child presented with chronic constipation and abdominal distension. Hirschsprung's disease was diagnosed on a rectal biopsy specimen, which included mucosa, muscularis mucosae, and submucosa in which no ganglion cells were detected. A transverse colostomy was performed. During the Duhamel pull-through operation three months later a descending colon full thickness biopsy specimen was reported to be ganglionic on frozen section. The colon at this level was therefore anastomosed to the anorectal junction. Histology of the 16 cm of resected rectosigmoid was reported as showing ganglion cells in the proximal and middle levels with a 3 cm long aganglionic distal segment.

Large bowel obstruction developed after closure of the transverse colostomy, requiring

Figure 4 Patient 3. Large bowel wall. An example of a cluster of large, sometimes gigantic, ganglion cells. (S-100 protein by immunoperoxidase method $\times 350$.)

Figure 5 Patient 3. Large bowel wall showing increased numbers of thick and tortuous nerve trunks. (S-100 protein by immunoperoxidase method $\times 175$.)

Figure 6 Patient 3. Large bowel wall showing hyperplasia and hypertrophy of the intermuscular plexus. (Haematoxylin-eosin stain $\times 350$.)

its reconstruction. Biopsy of specimens from left and right transverse colon showed an increased number and size of ganglion cells in both plexuses and the presence of thick cholinergic nerve trunks in the submucosa suggesting a diagnosis of hyperganglionosis. On review of the original specimen of excised rectosigmoid by the pathologist, very sparse ganglion cells were found in the section of its distal portion. The Duhamel operation was revised six months later, anastomosing ascending colon to the rectal stump, with a covering ileostomy. The entire resected colon showed the same histological changes as in the transverse colon, including the resection margins (figs 4–6). After closing the ileostomy the child remains well and has three bowel actions a day.

Discussion

Patients presenting with chronic constipation or with bowel obstruction in the neonatal period are frequently investigated to exclude Hirschsprung's disease, but hyperganglionosis may mimic this presentation.

Because of the similarity of appearance of the staining of the nerve fibre network in the lamina propria mucosae on acetylcholinesterase staining in Hirschsprung's disease and hyperganglionosis, it is essential to ensure that the suction rectal biopsy specimen contains adequate submucosa to confirm or exclude the presence of ganglion cells. In our first patient an erroneous initial diagnosis of Hirschsprung's disease was made because of the appearances of the lamina propria mucosae on an inadequate specimen. Meier-Ruge warned of this pitfall.¹⁹ The nerve network in hyperganglionosis is more prominent than normal but less prominent than that found in Hirschsprung's disease.

In two out of 10 of the cases reported by Munakata *et al* over 10 years the diagnosis of hyperganglionosis was made on acetylcholinesterase staining of a suction rectal biopsy specimen alone.¹⁴ We prefer to make the diagnosis when some other features that were mentioned by Nezeloff *et al* and Meier-Ruge are present on full thickness bowel specimens: hypertrophy and hyperplasia of the intermuscular as well as the submucosal plexus. In these three patients it took a period of one to four months and review of full thickness specimens before the condition was diagnosed with certainty. We suspected the condition in a further term baby unable to open her bowels without rectal washouts for the first four months of life in whom suction rectal biopsy appearances were suggestive of hyperganglionosis. However she recovered on conservative management and as there was no clinical indication for a full thickness rectal biopsy we were unable to confirm the diagnosis.

It could be argued that the diagnostic criteria for hyperganglionosis are subjective and 'observer dependent' so that, ideally, ganglion cell counts should be performed.^{10 20} However, having carried out a count of maximal number of ganglia per high power field in the rectal biopsy specimens of nine normal constipated children and our three patients (rectal biopsies

in the first two and a colonic biopsy in the third), there was too much overlap in the counts between the two groups to be useful. The histochemical and histological features of the condition are not all present on every specimen but we are persuaded that we noted sufficient of the features mentioned in the methods to confirm the diagnosis.

A hyperganglionic region of bowel existing proximal to an aganglionic segment in Hirschsprung's disease has been reported from several centres.^{8-12 14 15 21} These children may often present in the same way as our third patient, with bowel obstruction after the pull-through procedure.

There is a big discrepancy in the literature in the reported incidence of hyperganglioneosis. Colleagues of Meier-Ruge have suggested it may be as common as Hirschsprung's disease¹² or 20% that of Hirschsprung's disease.¹³ Garrett and Howard¹⁶ and Risdon and Malone²² propose its comparative incidence is less than 5% that of Hirschsprung's disease. This suggests different diagnostic criteria are being used.

Some authors report poor peristalsis in hyperganglionic bowel but with functional improvement over months or years.^{12 14 15 23} This is illustrated by patient 1 who presented with small bowel obstruction managed with an ileostomy. This was subsequently closed and the patient thrived with a temporary sigmoid colectomy, and when this was closed had normal bowel function despite persisting histochemical change. In the second patient, who presented with gross constipation, it was decided to perform total colectomy because the barium loopogram demonstrated an irregular calibre of the colon with slow transit. In the third patient, who thrived with a right transverse colostomy, despite gross changes in the appendix, a repeat Duhamel pull-through was performed with the right colon. The surgical management is therefore not the same as in Hirschsprung's disease, where the length of the aganglionic segment precisely dictates the extent of bowel resected.

In conclusion, hyperganglioneosis can mimic Hirschsprung's disease in its presentation. Acetylcholinesterase staining of suction rectal biopsy specimens is helpful in alerting the pathologist to the abnormality, but for differentiating it from Hirschsprung's disease adequate submucosa must be present. It is necessary to examine histologically more than one full thickness specimen of rectum or intestine to make a secure diagnosis of hyperganglioneosis. The surgical management of the patients is based on clinical and radiological

criteria, and staged treatment with temporary stomas is recommended.

- 1 Nezelof C, Guy-grand D, Thomine E. Les megacolons avec hyperplasie des plexus myenteriques. Une entite anatomo-clinique a propos de trois cas. *Presse Med* 1970;78:1501-6.
- 2 Alison F, Bocquet L, Schmelk P-H, Ploussard J-P. Hyperplasia des plexus myentericus. *Arch Fr Pediatr* 1974;31:315-25.
- 3 Retbi JM, Rosenstein-Retbi J, Gabilan JC. Megacolons avec hyperplasie des plexus myenteriques: revue de la litterature a propos d'un cas chez un nouveau-ne premature. *Revue Pediatre* 1979;15:34-9.
- 4 Weisgerber G, Sonsino E, Navarro J, Rivron M, Aigrain Y, Boureau M. Le syndrome 'intestin non fonctionnel' primitif chez l'enfant. Elements diagnostique et approche therapeutique des peristaltopathies digestives primitives autres que la maladie de Hirschsprung. *Chir Pediatr* 1980;21:107-16.
- 5 Meier-Ruge W. Ueber ein Erkrankungsbild des Kolons mit Hirschsprung-Symptomatik. *Verh Dtsch Ges Pathol* 1971;55:506-9.
- 6 Klos I, Maier WA, Morger R, et al. Die neuronale Kolondysplasie. *Z Kinderchir* 1978;38:53-4.
- 7 Gullotta F, Straaten G. Hirschsprungsche Krankheit mit gleichzeitige Aganglionose und sogenanntur neuronaler Kolondysplasie (Dysganglioneosis colica). *Z Kinderchir* 1977;20:42-9.
- 8 Puri P, Nixon HH, Mishalany H, et al. Neuronal colonic dysplasia: an unusual association of Hirschsprung's disease. *J Pediatr Surg* 1977;12:681-5.
- 9 Kessler S, Campbell JR. Neuronal colonic dysplasia associated with short-segment Hirschsprung's disease. *Arch Pathol Lab Med* 1985;109:532-3.
- 10 Scharli AF, Meier-Ruge W. Localised and disseminated forms of neuronal intestinal dysplasia mimicking Hirschsprung's disease. *J Pediatr Surg* 1981;16:164-70.
- 11 MacMahon RA, Moore CCM, Cussen LJ. Hirschsprung-like syndromes in patients with normal ganglion cells on suction rectal biopsy. *J Pediatr Surg* 1981;16:835-9.
- 12 Fadda B, Maier WA, Meier-Ruge W, Scharli A, Daum R. Neuronale intestinale Dysplasie. Eine kritische 10-Jahres-Analyse klinischer und biopsischer diagnostik. *Z Kinderchir* 1983;38:305-11.
- 13 Fadda B, Pistor G, Meier-Ruge W, Hofmann-von Kap-herr S, Muntefering H, Espinoza R. Symptoms, diagnosis, and therapy of neuronal intestinal dysplasia masked by Hirschsprung's disease. Report of 24 cases. *Pediatric Surgery International* 1987;2:76-80.
- 14 Munakata K, Morita K, Okabe I, Sueoka H. Clinical and histological studies of neuronal intestinal dysplasia. *J Pediatr Surg* 1985;20:231-5.
- 15 Pistor G, Hofmann-von Kap-herr S, Grussner R, Munakata K, Muntefering H. Neuronal intestinal dysplasia. Modern diagnosis and therapy—report of 23 patients. *Pediatric Surgery International* 1987;2:352-8.
- 16 Garrett JR, Howard ER. Development of the autonomic nervous system. In: Birnstock G, ed. *Ciba foundation symposium* 83. London: Pitman Medical, 1981:326-44.
- 17 Heaton ND, Garrett JR, Howard ER. The enteric nervous system: structure and pathology. In: Bannister R, ed. *Autonomic failure: a textbook of clinical disorders of the autonomic nervous system*. New York: Oxford Medical Publications, Oxford University Press, 1988:238-63.
- 18 Lake BD, Puri P, Nixon HH, Claireaux AE. Hirschsprung's disease. An appraisal of histochemically demonstrated acetylcholinesterase activity in suction rectal biopsy specimens as an aid to diagnosis. *Arch Pathol Lab Med* 1978;102:244-7.
- 19 Meier-Ruge W. Hirschsprung's disease: its aetiology, pathology and differential diagnosis. *Curr Top Pathol* 1974;59:131-79.
- 20 Simpson E, Kahn E, Kenigsberg K, Duffy L, Markowitz J, Daum F. Neuronal intestinal dysplasia: quantitative diagnostic criteria and clinical management. *J Pediatr Gastroenterol Nutr* 1991;12:61-4.
- 21 Lassman G, Wurnig P. Lokale Ganglionzellhyperplasie in der Submucosa am oralen Ende des aganglionaren Segments bei Morbus Hirschsprung. *Z Kinderchir* 1973;12:236-43.
- 22 Risdon RA, Malone M. Paediatric gastrointestinal disease. In: *Recent advances in pathology*. Edinburgh: Churchill Livingstone, 1989:223-49.
- 23 Sacher P, Briner U, Stauffer UG. Zur klinischen Bedeutung der neuronalen intestinalen Dysplasie. *Z Kinderchir* 1982;35:96-7.