Adynamic bowel syndrome

Report of a case with disturbance of the cholinergic innervation

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SUMMARY A case of adynamic bowel syndrome is described. Full thickness biopsies of the large bowel showed the presence of ganglion cells, no acetylcholinesterase positive nerves in the lamina propria, submucosa or among the smooth muscle cells of the circular and longitudinal muscle coats, and absence of the argyrophil plexus. Electron microscopic examination showed replacement of the normal axon bundle by vacuolated tracts with small round bodies in one area—probably viral. Neuronal cytoplasm also showed similar vacuolation. It is suggested that the damage to the cholinergic innervation may be caused by a neurotoxic agent.

Adynamic bowel was described by Nixon in 1966 as a clinical condition simulating Hirschsprung's disease but with normal histopathology; the most striking feature that is characteristic of this entity being the absence of peristalsis. Recently, Kapila *et al.* (1975) described four cases of adynamic bowel where examination of the colon by classical histological methods failed to reveal the underlying pathology of this condition.

We recently encountered an infant with all the features of adynamic bowel syndrome where ganglion cells were seen in the rectal biopsies but on further examination of the colon by histochemical and electron microscopic studies a disturbance in the cholinergic innervation was found.

Case report

G.B., a 3.6 kg male infant, was born on 3 March 1975 to a 33 year old gravida 4, para 4 mother who had an uneventful labour and delivery. Pregnancy was complicated by pre-eclamptic toxæmia. The baby was breast fed for the first three months and then changed to Cow and Gate Formula V feeds. He passed normal stools while on breast feeds but, soon after the bottle feeds were started, he began passing scanty amounts of pellet-like stools. He continued to feed and gain weight normally until on 3 September 1975 he was admitted to the local hospital with a 10 day history of absolute constipation,

vomiting, and intermittent screaming attacks. On examination the abdomen was moderately distended; faecal masses were palpable in the whole of the colon. The child was treated with rectal irrigation which yielded no result. The patient was transferred the next day to the Hospital for Sick Children, Great Ormond Street, where physical examination revealed a mildly dehydrated infant with normal cardiovascular and respiratory system. There was moderate abdominal distension; the ascending, transverse, and descending colon were palpable with hard faecal masses. On digital examination the rectum was empty; high up in the rectum hard, rock-like faeces were palpable.

Laboratory investigations revealed: haemoglobin 12.7 g/dl, white cell count $12,800 \text{ mm}^{-3}$, platelets normal, blood urea and serum electrolytes normal. Urine showed traces of protein, red cells less than 1 mm^{-3} , and a mixed growth on culture. Plasma thyroxine, gastrin, and calcitonin were within the normal range.

Plain radiography of the abdomen showed a distended large bowel loaded with faecal material. Barium enema was suggestive of a short segment Hirschsprung's disease. Anorectal manometry showed absence of normal internal sphincter inhibitory response to rectal inflation, suggestive of Hirschsprung's disease. Suction rectal biopsy, however, showed ganglion cells to be present in the submucous plexus. In view of the ganglionic rectal biopsy Hirschsprung's disease was thought to be excluded and the infant was transferred back to the

local hospital for rectal irrigation.

The infant's condition deteriorated in spite of daily irrigations and he was readmitted on 4 October 1975 for further reassessment. Examination revealed a pale, malnourished infant; the abdomen was grossly distended with faecal masses still palpable in the whole of the colon. A barium meal and follow-through was normal except for dilated large intestine.

A repeat suction biopsy was performed. Again ganglion cells were seen and, on histochemical staining using the intensification method of Hanker *et al.* (1972) as described by Lake (1976), the numbers and distribution of acetylcholinesterase positive nerves in the lamina propria and muscularis mucosae were normal. A plain abdominal radiograph on 22 October 1975 showed an enormous amount of barium still present in the large bowel even 12 days after the previous barium study. The child was then treated with large doses of Senokot (a standardised preparation of sennosides A and B), rectal irrigation, and phosphate enemas which produced no improvement in his clinical condition. A full-thickness rectal biopsy was performed; ganglion cells were again present but on silver staining there was absence of

the argyrophil plexus. Because of this histological finding and also because rectal irrigations and aperients had produced no improvement in his clinical condition, it was decided to perform an ascending colon loop colostomy on 29 October 1975. A full thickness biopsy from the ascending colon was taken at the time of operation which showed the presence of normal appearing ganglion cells. Again there was absence of the argrophil plexus. On histochemical staining no acetylcholinesterase positive nerves could be demonstrated in the lamina propria, submucosa, or among the smooth muscle cells of the circular and longitudinal muscle coats (Fig. 1). Electron microscopy of the biopsy showed normal smooth muscle cells. There were spaces between bundles of muscle cells which appeared to be where nerve fibres had been or should have been situated. The cells (Figs 2 and 3) in these spaces were similar to Schwann cells. The spaces were lined by cell membranes. In one field there were some small round bodies of the order of 900 nm in diameter, each containing eight or 10 osmophilic inclusions of 200 nm diameter (Fig. 4). One small group of ganglion cells was identified. The cytoplasm

Fig. 1 Cryostat section stained to demonstrate acetylcholine esterase activity. A nuclear counterstain has been given. Scale mark 200 μ m. (a) Normal colon. Note the ganglia (large arrow) and the numerous nerves in the circular muscle coat (small arrows). (b) Colon from patient. Ganglia are present but no nerve fibres are seen in the muscle coats.

Fig. 2 *Electron micrograph: (a) Only vacuolated tracts remain where axonal bundles should be situated. The smooth muscle cells appear normal. Scale mark 2 μ m. (b) Normal colon. Normal nerve trunk between muscle cells. For comparison with (a). Scale mark 2 μ m.*

Fig. 3 *Electron photomicrograph: as Fig. 2a. Scale mark 5 μ m.*

Fig. 4 *Electron photomicrograph: two groups (arrows) of possible viral particles are present in the distended axonal spaces. Scale mark 0.5 μ m.*

of the neurons showed patchy changes, with some areas having the normal appearance and other areas showing marked vacuolation.

After the colostomy his general condition improved. He started passing normal stools through the proximal stoma but the distal colon remained full of hard faeces still containing barium on repeated radiography. Only after prolonged rectal irrigations with Diotyl medo (diotyl sodium sulfosuccinate) and saline was it possible to empty the colon to a reasonable extent.

The child was discharged on 20 November 1975 but readmitted on 14 January 1976 because of recurrent prolapse of the colostomy. His general condition had much improved and he had begun to gain weight. In view of the prolapsing colostomy, it was decided to transform the loop colostomy into an end ileostomy; this was performed on 21 January 1976.

The infant is developing normally and, when last seen on 30 April 1976, aged 1 year 2 months, he was on the 50th percentile of weight.

Discussion

Although our patient had many features of Hirschsprung's disease the presence of ganglion cells in several suction rectal biopsies and the presence of a normal number and distribution of acetylcholinesterase positive nerves in the lamina propria, muscularis mucosae and submucosa excluded this diagnosis. However, no circular or longitudinal muscle tissue was obtained at that time. Later studies on biopsies taken from the ascending colon at the time of the colostomy and a full thickness rectal biopsy showed that the nerve network linking ganglion cells in the intramural plexus and elsewhere was not present, although ganglion cells were present and appeared normal by light microscopy.

There are two possible explanations for this. Firstly, there could have been a failure in development of nerve fibres, but for this to have happened there should also have been an accompanying lack of ganglion cells and the patient would have developed symptoms at an earlier time. An alternative explanation is that the nerve plexus developed normally with normal bowel function until 6 months of age when a neurotoxin or neurotoxic agent attacked the intramural nerve plexus. Evidence in support of this is found in the ultrastructure of the biopsy taken from the colon. Tracts where normal bundles are usually situated are empty and the remaining cells (?Schwann cells) have grossly vacuolated cytoplasm. The neurons of the intramural plexus, although appearing normal by light microscopy, also showed vacuolation of their

cytoplasm similar to that found in the Schwann cells and axons. In one area some bodies which could be interpreted as viral, were found in the vacuolated tracts. The absence of intact nerve fibres is also confirmed by silver stains which showed no argyrophil plexus. This is in contrast with the patient described by Kapila *et al.* (1975) in whom the argyrophil plexus was intact. It is not possible to determine whether the neuronal changes are primary or secondary, as only a few neurons could be found at electron microscopy despite extensive sectioning.

McElhannon (1959) selectively destroyed the myenteric plexus in dogs by injecting Urokon (sodium 3-acetamido-2,4,6, triiodobenzoate) into the inferior colic artery, producing symptoms of Hirschsprung's disease and demonstrating the absence of peristaltic activity in the aganglionic bowel on electromyography. Similarly, Imamura *et al.* (1975) produced colonic aganglionosis experimentally in the rat by intraluminal filling under tension of the colorectum with 0.01% mercuric chloride in normal saline. The colonic aganglionosis thus produced by the combined effect of ischaemia and the neurotoxic action of absorbed mercuric chloride resulted in the formation of a definite contracted segment of bowel which was aperistaltic. These results contrast with the observations in patients with Chagas' disease in whom the myenteric plexus is believed to be destroyed by the toxins of *Trypanosoma cruzi* producing an aperistaltic dilated bowel. In these cases the argyrophilic plexus is variably affected, being present in some areas and absent in others (Smith, 1967).

We feel that one cause of the adynamic bowel syndrome may be neurotoxic, in which the cholinergic nerves and possibly neurons are attacked. We consider it important that tissues from all cases of Hirschsprung's disease and clinically allied disorders should be studied not only histologically but also by histochemical methods to demonstrate the cholinergic nerves.

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