A Vascular Cause for Hirschsprung's Disease?

In this issue of GASTROENTEROLOGY Taguchi et al. describe fibromuscular dysplasia of the arteries in 8 of 25 children with Hirschsprung's disease (1). The reason for the loss of ganglion cells in the gut and the cause of the thickened muscle in the smooth wall of the arteries are both unknown, so combining two rare pathologies of undetermined etiology may just confuse rather than help us. However, ischemia may be a common denominator because it has been postulated as a possible mechanism for the two pathologies, both of which involve smooth muscle. A summary of the relevant research in fibromuscular dysplasia and aganglionic bowel, together with the restatement that there may be a vascular ischemic cause for both Hirschsprung's disease and achalasia, may produce more circumstantial evidence that will fit in with this hypothesis (2).

Fibromuscular dysplasia was first described in 1938 by Leadbetter and Burkland (3) in the renal artery, producing unilateral renal disease. Palubinskas and Ripley (4) demonstrated fibromuscular hyperplasia by angiography in extrarenal arteries in 1964, which was later confirmed pathologically. By 1982, 1100 cases, including 300 cranial lesions, had been described in a review article on fibromuscular dysplasia and the brain (5). The pathology consists of a fibroblastlike transformation of smooth muscle cells that is classified according to the dominant layer of the arterial musculature. Approximately 90% involve the media and only 5% involve the intima. Angiographically they are divided into multifocal, focal, and tubular. A complication may be a microaneurysm. The etiology is unknown but vascular lesions caused by obstruction of the vasa vasorum have been produced experimentally (6). Clinically, ischemic lesions of the bowel have been found associated with fibromuscular dysplasia in the small bowel (7) and in ischemic proctitis (8). The problem is a chicken and egg one—which came first? The association does not necessarily imply etiology and it has been noted that the arterial lesions increase with age (9). If there were 1100 cases of fibromuscular dysplasia described by 1982, more will be found and they must be studied in detail to find out whether there are lesions of the vasa vasorum, which muscle layer is involved, and what the nerve supply is like.

In Hirschsprung's disease there is usually a narrow segment with no ganglion cells, a transitional zone with a few cells, and proximal gut with normal neurons, dilated because of the distal obstruction. The overgrowth of nerve fibers fills the spaces between the muscles and in the submucosal layer where Auerbach's and Meissner's nerve plexus should be. Most agree that these fibers, in simplistic terms, are seeking connections with ganglion cells that are not present. The normal neurons are not uniform and are of many different types, all arising from the pluripotential neural crest (10). Were they never present or were they there but subsequently destroyed? Congenital neural crest lesions would explain their original absence and vascular lesions could explain their later destruction. Another theory, based on experimental work in the guinea pig (11), suggests that the aganglionic area either lacks a substance that promotes or contains a substance that prevents migration of ganglion cells into that area.

Ganglion cell destruction by ischemia is based on the original work of Cannon and Burket (12). Of the four basic tissues in the gut—connective tissue, epithelium, muscle, and nerve—the latter is the most sensitive to anoxia and can never regenerate (13). In the brain anoxia destroys nerve cells in minutes but in the gut the optimum time taken to destroy neurons is 4 hours.

Aganglionic bowel has an anatomic distribution based on the susceptibility of the gut to blockage of its arterial supply, and this is especially so in the very early days of the embryo before the diaphragm has descended. Achalasia and Hirschsprung's disease are situated at both ends. Aganglionic megaduodenum, which is extremely rare, is at the junction of the celiac axis and superior mesenteric arterial blood supply. Hirschsprung's disease with various lengths of bowel affected is distributed according to the arterial blood supply. In the very long segment type of Hirschsprung's disease, involving all the large bowel and the small bowel up to the duodenojejunal flexure and in which there is no overgrowth of nerve fibers as seen normally in the shorter segments, the
distribution of the lesion is in that part of the gut supplied by the superior and inferior mesenteric arteries. The original vascular hypothesis (2) suggested three types of congenital gut lesion that may follow occlusion of the blood supply. The type depended on the duration of the ischemia, which produced different degrees of infarction and scar tissue: (a) atresia (with or without a band), (b) stenosis, and (c) aganglionic bowel. If this hypothesis is true, the anatomic distribution should be approximately similar. Rectal, esophageal, and duodenal atresia exist in the same anatomic situations as their aganglionic counterpart and there is some evidence to support a transitional zone of aganglionic bowel between the narrowed atresia and normal bowel. The frequency with which atresia and aganglionic bowel exist at these anatomic sites varies and has to be explained by local differences in sensitivity to anoxia and differing responses to the reduction in ganglion cell numbers. Evidence for this comes from Chagas’ disease where the ganglion cell loss may be equal in the colon and esophagus—but megacolon is much more common than megasophagus (14). Additionally, a long stage of decomposition after ganglion cell loss is seen in Chagas’ disease. The acute phase of the illness occurs in infants but the manifestations of the chronic illness are seen 20 or 30 years later (14), which might account for achalasia being a congenital lesion in spite of the peak incidence being in the third decade.

It has been suggested that the ischemia, which could cause Hirschsprung’s disease, results from excessive rotation of the normal volvulus that the gut undergoes in its early development between the fifth and tenth week of intrauterine life. At this stage there is a large umbilical hernia containing most of the gut, which is only fixed at both ends. The normal 270° counterclockwise rotation results in the adult position with the ascending colon and duodenum fixed to the posterior abdominal wall on the right side. Fixation only occurs late but, in the first 2 months when ganglion cells have already migrated to the gut wall, ischemia could occur if the normal rotation became a volvulus and caused gangrene at the base of the loop. This would explain why the ganglion cell loss appears localized to the gut wall and does not involve the bladder. Any lesion of the neural crest would have to be very localized to only affect a short segment of large bowel.

The ischemic theory of ganglion cell destruction is based on experiments confirming Cannon’s original work (15–18). The hypothesis is based on circumstantial evidence and would be difficult to prove without experiments on animals at the early stages of development. Barnard (19) did the original work in Minneapolis, producing atresia and stenosis of the small bowel by operating on the gut of puppies while they were still in utero. Stenosis has been described after vascular lesions were made on the small bowel in the natural umbilical hernia of the chick embryo still in its shell (20). Further details are required to document the transitional zone between atresia, stenosis, and aganglionic bowel (21,22). In rectal atresia this transition has been calculated to occur in 3.4% of all cases (19), but the percentage increases when type 3 atresia alone is considered (20). Hirschsprung’s disease should be examined to confirm its anatomic distribution on an arterial blood supply basis, and the very rare cases of total small and large bowel Hirschsprung’s disease should be studied by special nerve stains because these particular patients seem to lack the overgrowth of nerve fibers, and only have empty spaces where ganglion cells should be (23).

There is much more work to be done to test the different hypotheses. Ischemia can be caused by a volvulus, intussusception, obstruction in a hernia, or any cause of intraluminal arterial obstruction, and evidence of these mechanisms might be present in atresia, stenosis, or aganglionic bowel. At the same time, other theories must be investigated. Craniocaudal migration of nerve cells certainly occurs (24) and can be interrupted. Malrotation in Hirschsprung’s disease has been described (25) and there are probably many more cases seen but not reported in the literature. Arterial lesions have been found before in Hirschsprung’s disease (26), but the finding of fibromuscular dysplasia as a specific arterial pathology should encourage a further search for arterial abnormalities in the congenital gut lesions of atresia, stenosis, and aganglionic bowel, and specifically in the transitional zone. Destruction of ganglion cells in the gut by temporary ischemia may be one of nature’s most perfect crimes and we need every tiny scrap of evidence to solve it.

RICHARD EARLAM, M. Chir. F.R.C.S.
Consultant Surgeon
The London Hospital (Whitechapel)
London, England

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