Diagnosis and surgical treatment of isolated hypoganglionosis

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Background: **Some patients suspected with Hirschsprung's disease (HD), however, were diagnosed as having isolated hypoganglionosis according to the updated pathohistologic methods. This study was undertaken to investigate the diagnostic methods and the therapeutic results of isolated hypoganglionosis in children.**

Methods: **A retrospective analysis was made on 17 patients with isolated hypoganglionosis (hypoganglionosis group) identified pathologically after operation. The data included clinical presentations, barium enema, anorectal manometry, histochemical staining for acetylcholinesterase (AChE) before operation, histological results after operation and follow-up outcomes. The data of hypoganglionosis with HD (HD group) were compared retrospectively.**

Results: **Common complaint of the patients with hypoganglionosis and HD was intractable constipation. Barium enema showed typical narrowing and distended segment of the colon in 9 patients in the hypoganglionosis group (9/16) and in 15 patients in the HD group (15/18). In the hypoganglionosis group, in 15 patients who underwent anorectal manometry only 5 showed absent rectal anal inhibitory reflex, significantly lower than the rate in the HD group (17/18) (P<0.05). From 16 patients in hypoganglionosis group, positive staining for AChE was noted in 3 patients (3/16, 18.8%), significantly lower than that in the HD group (16/18, 88.9%) (P<0.05). Thirteen patients in the hypoganglionosis group received subtotal colectomy, while only 5 patients needed subtotal colectomy in the HD group. In the hypoganglionosis group, except 2 patients who suffered from mild enterocolitis after operation and recovered after conservative therapy, all patients recovered uneventfully without wound dehiscence, intestinal fistula, fecal incontinence or constipation recurrence. In the HD group, one patient suffered from anastomotic leak and got secondary operation, one patient had anastomotic stricture at 1 year after operation and recovered by dilatation, and other three patients suffered from mild enterocolitis after operation and recovered after conservative therapy.**

Conclusions: **Hypoganglionosis is a common disease, and could be finally confirmed by full-thickness biopsies in different bowel segments. The resection range can be estimated according to barium enema and 24-hour delayed X-ray findings, by which the satisfactory result in short-term follow-up can be obtained.**

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Introduction

Intractable constipation is common in childhood with many causative factors. Most researches have focused on the diagnosis and treatment of Hirschsprung's disease (HD), and some found that Hirschsprung's disease-allied disorders (HDADs) account for not a low proportion in children with intractable constipation.[1] Hypoganglionosis is a kind of HDADs, and few reports concentrated on its diagnosis and treatment.[1] Some patients suspected with HD, however, were diagnosed as having isolated hypoganglionosis after operation according to the updated pathohistologic methods. To find the clinical features of patients with isolated hypoganglionosis and their response to surgical procedures, we studied 17 patients who had been treated at the Department of Pediatric Surgery of Tongji Hospital between January 2004 and April 2006.

Methods

Subjects

Forty-five patients with neuronal intestinal diseases (NIDs), who had been hospitalized at our department

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between January 2004 and April 2006, were studied. All the patients complained of intractable constipation. Pathohistologically, they were classified into HD, isolated hypoganglionosis, intestinal neuronal dysplasia (IND), HD associated with hypoganglionosis and HD associated with IND. HD was defined as a form of absence of ganglion cells in the submucosal and intramuscular layers of the distal colon. Isolated hypoganglionosis was considered a state in which the number of ganglia in the myenteric plexus per millimeter colon is less than 1.52 according to the criteria introduced by Li and Zhu.[2,3] Intestinal neuronal dysplasia (IND) was diagnosed with the qualification of 15%-20% giant ganglia with more than 8 nerve cells in 30 sections from a single specimen according to Meier-Ruge's report.[4] HD associated hypoganglionosis was defined as an oligoganglionic segment proximal to a segment of typical aganglionosis. HD associated with IND was defined as an IND segment proximal to a segment of aganglionosis.

Of the 45 patients, 18 had HD, 17 had isolated hypoganglionosis, 6 had IND, 2 had HD associated with hypoganglionosis, and 2 had HD associated with IND. The data of isolated hypoganglionosis (hypoganglionsis group) and Hirschsprung's disease (HD group) were compared retrospectively in this study.

Among the 17 patients with isolated hypoganglionosis, 10 were males and 7 were females, aged 28 days to 17 years (average: 48 months). All the patients referred to our hospital because of refractory constipation except one 28-day-old female neonate for acute intestinal obstruction, who received ileostomy to relieve the symptoms of intestinal obstruction. Of the 18 patients with HD, 12 were males and 6 were females, aged 30 days to 5 years (average: 24 months).

Preoperative examination

Sixteen of the 17 patients with isolated hypoganglionosis and all the 18 patients with HD underwent barium enema X-ray examination to see if there was a narrow or dilated segment, or haustra disappearance of the sigmoid colon. Twenty-four hours later, X-rays were taken again to evaluate barium retention.

After informed consents were obtained from the parents, 16 patients in the hypoganglionosis group and 18 patients in the HD group underwent suction biopsy of the rectal mucosa for the qualitative evaluation of acetylcholinesterase (AChE) activity by histochemical staining. The suction biopsy was performed at 2 cm and 5 cm above the dentate line.[5] AChE activity was evaluated using the Karnovsky-Roots method with some modifications.[6] AChE reaction in the mucosal layer was evaluated according to the following features: (1) negative AChE reaction: no AChE-positive nerve fibers in the lamina propria mucosae and muscularis mucosae; (2) positive AChE reaction: there are AChE-positive nerve fibers in the muscularis mucosae, and some fibers run transversely to the lamina propria mucosae, or a thick network of AChE-positive nerve fibers in the muscularis mucosae and lamina propria mucosae.

Fifteen of the 17 patients in the hypoganglionosis group and 18 patients in the HD group underwent anorectal manometry. The method for anorectal manometry to detect anorectal inhibitory reflex and reflex threshold was described previously.[7] The threshold of healthy infants was 15-20 ml, and that of neonates was 10-15 ml.[7]

Surgical procedures

All patients except the neonate were treated by saline colonic irrigation, enema, high dose lactulose, and oral paraffin oil for 4 months at least. Since there was no clinical improvement, operative procedures were taken. Dilation and disable mobility of colon were manifested by barium enema and 24-hour delayed X-ray, indicating a damaged segment. If there was no obvious retention of barium in the colon for more than 24 hours or retention was just in the sigmoid colon and rectum, the patients would receive megarectosigmoid resection, followed by pulling through the descending colon and anastomosed to the rectum or anus. If barium detained in the proximal descending colon, subtotal colectomy would be possible, while rotating the ascending colon anticlockwisely and pulling down for anastomosis. The patients were not subjected to biopsies during operation.

Eleven of the 17 patients with isolated hypoganglionosis received one-stage rectal colon heart-shaped anastomosis. The heart-shaped anastomosis, an open operation designed by us, takes the transanal route for anastomosis. It has been used in our department since January 1986. The heart-shaped anastomosis applied to the patients with hypoganglionosis was the same as HD patients. The procedure could effectively prevent the occurrence of postoperative complications and significantly decrease the incidence of incontinence or soiling and recurrence of constipation after surgery.[8] In the other 6 patients, 2 had Soave transanal endorectal pull-through, 1 had Ikeda procedure (total colectomy), 1 (a neonate) had emergency ileostomy, closed ileostomy and total Ikeda procedure (colectomy) 6 months later, 1 had endorectal pull-through, and 1 had laparoscopic-assisted colon resection.

Statistical analysis

The data were statistically analyzed using SPSS 14.0 (SPSS Inc., Chicago, IL). Comparison was made between groups using the Chi-square test. A *P* value less than 0.05 was considered statistically significant.

Results

Barium enema

In the 17 patients with isolated hypoganglionosis, 9 (52.9%) presented a narrow distal segment and a dilated proximal segment; 2 of the 9 patients found with classic funnel-shaped dilation at the level of the transmission zone. In the other 8 patients, the barium enema findings were uncertain, but a delayed film after 24 hours showed barium retention, suggesting a disorder of colonic motility. Thirteen patients received subtotal colectomy because of barium retention in the proximal descending colon for more than 24 hours. The other 4 patients were subjected to left colectomy for barium retention in the distal descending colon for longer than 24 hours.

Compared with patients with isolated hypoganglionosis, 15 (83.3%) of the 18 HD patients presented classic narrow distal segment and dilated proximal segment. There was no significant difference between the two groups ($P>0.05$) (Table). However, barium retention in the proximal descending colon after 24 hours in the HD group was 5, significantly lower than that in the hypoganglionosis group. All these 5 patients underwent subtotal colectomy with heart-shaped anastomosis, and the other 13 patients underwent left colectomy with heart-shaped anastomosis.

Anorectal manometry

In the 15 patients with isolated hypoganglionosis who had undergone anorectal manometry, anorectal reflex waves disappeared in 5 (33.3%) patients, reflex thresholds of the 10 patients were 28±5 ml (the normal value of reflex threshold is 10-15 ml in neonates and 15-20 ml in infants). In the 18 HD patients, 17 patients (94.4%) showed disappearance of anorectal reflex waves ($P<0.05$). The value increased significantly compared with that of normal children (7.8±3 ml, $P<0.05$) (Table).

Rectal suction biopsy and AChE histochemical staining

Three of 16 patients in the hypoganglionsis group (3/16, 18.8%) were positive of rectal mucosa acetylcholinesterase (AChE) activity, significantly lower than that of the HD group (16/18, 88.9%) ($P<0.05$) (Table).

Surgical outcomes

Thirteen patients received subtotal colectomy, and 4 patients subjected to left colectomy in the hypoganglionosis group.

Complications such as anastomotic leak, anastomotic stricture, wound split and constipation relapse were not seen in the patients with isolated hypoganglionosis in our study. The patients receiving subtotal colectomy had frequent and loose stools due to impaired colonic water absorption. Defecation for 3 to 7 times per day was common in the early postoperative period. But the patients receiving left colectomy showed normal frequency and consistency of defecation even in the early postoperative period.

One patient with HD was complicated by anastomotic leak, and recovered by secondary operation. No other short-term complications were noted in HD group.

Histological examination after operation

Resected colon specimens from the patients with isolated hypoganglionosis showed no transition to a normal innervated colon. Fifteen of the 17 patients were diagnosed with significant deficiency of ganglia in the myentric plexus. The neonate was diagnosed with total colonic hypoganglionosis. The other 2 patients, who were subjected to subtotal colectomy using one-stage heart-shaped anastomosis, were detected with a deficiency of ganglias both in the myentric and submucosal plexus. The end of the resected bowel proximal to the normal bowel had normal ganglias.

Follow-up results

The 17 patients with isolated hypoganglionosis were followed up at the Outpatient Department for two years up to now. They had voluntary bowel movements and normal social activities. The frequency of defecation in the patients reduced to 1-3 times per day, and stool texture became normal in no longer than 6 months after operation.

Fecal incontinence was not observed in these patients. Enterocolitis occurred in 2 patients: one in two months after operation and the other 1 year later. They were cured using conservative antibiotic therapy.

Table. Comparison of clinical tests between isolated hypoganglinosis and Hirschsprung's disease

Clinical tests	Hypoganglionosis	Hirschsprung's disease	χ^2	P
Barium enema Narrow distal segment and dilated proximal segment presented	9/16 (52.9%) cases	15/18 (83.3%) cases	3.044	0.134
Anorectal manometry Anorectal reflex waves disappeared	5/15 (33.3%) cases	17/18 (94.4%) cases	15.190	<0.05
AChE histochemistry Positive	3/16 (18.8%) cases	16/18 (88.9%) cases	18.662	<0.05

Three patients were suffered from enterocolitis after operation in HD group, and recovered after conservative therapy. One patient suffered from the anastomotic stricture at 1 year after operation and recovered by dilatation.

Discussion

In 1964, Bentley[9] first reported 5 cases of hypoganglionosis in 22 cases of megasigmoid and megarectum. However, the understanding of hypoganglionosis is controversial because the diagnostic criteria are not strictly defined around the world. Hypoganglionosis is characterized by a reduced number of myenteric ganglia, a low AChE activity in the lamina propria, and hypertrophy of the muscularis mucosae and circular muscle.[10] Holschneider et al[11] estimated that about 50% of all patients with clinical symptoms of HD have classical aganglionosis, and further 20%-40% of them have IND. Hypoganglionosis as an isolated disease represents only 5% of NID cases. The rest may have combined forms of or unclassified dysaganglionosis. The diagnostic criteria of hypoganglionosis are controversial, and reported morbidity is conflicting, even as low as 5% for colonic neuromuscular diseases.[10,12]

Recent investigations have provided lots of information about histopathological manifestations of hypoganglionosis, which may be useful for the establishment of commonly accepted diagnostic criteria. In 1999, Meier-Ruge et al[13] found that in patients with hypoganglionosis, the number of nerve cells was only about 40% of a normal innervated colon. The distance between the ganglia were doubled (hypoganglionosis: 421±98 μm; normal: 174±60 μm). The mean area of the ganglia in hypoganglionosis was three times smaller than the normal innervated colon (hypoganglionosis: 8.48±2.40 mm^2; normal: 21.88±5.12 mm^2). Another study also introduced the similar histopathologic manifestation mentioned above.[11] Shi et al[14] found the number of the ganglia in cross-section area per millimeter colon reduced to 10% of the normal. Zhu et al[3] found the number of ganglia in the myenteric plexus per millimeter colon was 1.52 (24.3% of the normal colon). In the ganglion cross-section area per millimeter colon the number was 5.61 (17.28% of the normal). According to the criteria, 17 patients (37.8%) had isolated hypoganglionosis in the 45 NID patients in this study. It may be due to the preference of the patients to choose the hospital they trust, but it suggests that hypoganglionosis should not be a rare condition.[5,10,12] Shi et al[14] reported the morbidity of isolated hypoganglionosis was 21.6% (11 of 51 patients with NID), which indicates that the incidence is not low in China.

Hypoganglionosis may take place as an isolated entity or exist proximal to a segment of typical aganglionosis, the transitional zone in HD. In hypoganglionosis associated with HD, there is a decrease in the number of ganglion cells in the submucosal and myenteric plexuses between the aganglionic and the normal segment. Increased AChE activity is seen in the mucosa of the distal oligoganglionosis segment.[12] However, isolated hypoganglionosis is characterized by deficiency of nerve cells in the myentric plexus and sometimes in the submucous plexus. According to Meier's report, isolated hypoganglionosis of the colon showed lower numbers of nerve cells and ganglia than Hirschsprung-associated hypoganglionosis.[13,14] Toguchi et al[15] reported that hypoganglionosis could be divided into 2 distinct entities as congenital and acquired hypoganglionosis, and histological findings and clinical characteristics of the 2 types of hypoganglionosis were partly different. Histologically, the number of ganglion cells in congenital hypoganglionosis was extremely small, and their size was also small in the neonatal period. The size of the Auerbach plexus was also small. Chronologically, the diameter of the nucleus of ganglion cells increased over time, but their numbers did not increase at all. Acquired hypoganglionosis was characterized as a degeneration and decrease in the number of ganglion cells. The size of the Auerbach plexus was preserved. The number of ganglion cells decreased, whereas the number of glial cells increased in the Auerbach plexus. Clinically, the onset of symptoms of congenital hypoganglionosis was identified at birth with poor prognosis. Whereas acquired hypoganglionosis occurred in elderly patients, and the prognosis was satisfactory after an appropriate resection of the affected bowel. The clinical spectrum of the 28-day-old female neonate in our patients was consistent with that of congenital hypoganglionosis.

In the patients with HD, short-segment aganglionosis may be associated with long-segment hypoganglionosis.[16] Most patients suffer from constipation even after operation due to insufficient resection of hypoganglionosis segment proximal to the aganglionosis segment.

Isolated hypoganglionosis can be categorized as mild type and severe type according to the severity of clinical symptoms.[10] The mild type is a condition involving a small area in older children. It has a good prognosis when treated conservatively or by surgical intervention (sphincterotomy or pull-through). The severe type is a condition which is present from birth, affects the small intestine, and has a poor prognosis even after surgical intervention. In our patients with isolated hypoganglionosis, 16 were of mild type, and 1 was of severe type. One neonate of severe type was admitted

to our department because of abdominal distention and constipation, and was subjected to ileostomy immediately. Six months later, we closed ileostomy and did total colectomy. Total colonic hypoganglionosis was pathologically diagnosed. Mild encopresis occurred in the first month after operation, and alleviated half a year. The patient visited us again for enterocolitis after 2 months. The other 16 patients who were older than 4 weeks presented with intractable constipation.

A few of reports described the radiological features of Hirschsprung's disease and allied disorders. The radiological findings of HD and HDADs appear to be similar.[17,18] In our series, the classic features were presented in 9 of the 16 patients with hypoganglionosis (52.9%) and 15 of the 18 patients with HD (83.3%). There was no significant difference in radiological features between hypoganglionosis and HD patients (P>0.05). The reason may be the inadequate number of patients demonstrating radiological difference between the two groups. Different from previous reports, anal manometry demonstrated the existence of internal anal sphincter relaxation, but the pressure profile of the anal canal was obviously elevated in contrast to normal children, which indicated damage of rectal function.[17]

Since conservative therapies can not alleviate symptoms effectively, operative treatment is essential.[9] The preoperative assessment of barium transmitting offers an opportunity to identify the range of impaired segment. If there is no barium retention in the colon for longer than 24 hours or just in the sigmoid colon and rectum, megarectosigmoid resection is feasible. If 24-hour delayed X-ray findings indicate obvious dilation of the proximal colon, rigid appearance of the colon, peristalsis of colon disappearance, and barium retention in the descending colon or above the segment for longer than 24 hours, subtotal colectomy should be taken into consideration.

In the Fourth International Symposium on Hirschsprung's disease and related neurocristopathies held in Sestri Levante, Genoa, Italy, on April 22 to 24, 2004, participants reached a consensus on the need of intraoperative biopsy, but there are controversies over the use of staining techniques (H&E or histochemical staining like LDH, NADPH-d, and nonspecific esterase).[19] Additionally, correct intraoperative pathological diagnosis depends on pathologist's experience. In our series, resection range is estimated according to the length of residue barium column on the 24-hour delayed X-ray. Although the way is shown to be effective in short-term follow-up, long-term follow-up is required to evaluate whether it is effective or not. Additionally, some investigators find that severe type has a poor prognosis.[10]

The etiology of hypoganglionosis remains unclear. The low-expression of neural cell adhesion molecules and synaptophysin on neurofibers in intestinal smooth muscles and mucosa in hypoganglionosis has revealed that hypoganglionosis is a disorder of neuromuscular junction.[20] No other evident mutation of the RET or GDNF in hypoganglionosis contributes to the pathogenesis of hypoganglionosis.[21] C-kit positive Cajal cells (ICC) are reduced and sparse in the intestinal wall.[22,23] Interstitial cells of Cajal as intestinal pacemakers are required for normal intestinal motility. Dissociated ICC has the ability to produce an electrical slow wave and is the source of smooth muscle rhythmic electrical activity in the normal intestine. Although many efforts have been made to detect the etiology and pathophysiology of hypoganglionosis, further study is necessary.

In conclusion, isolated hypoganglionosis may exist as a disease different from HD. Further investigations of etiology, diagnosis and treatment should be done to improve the prognosis of the disease.

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References

1 Puri P. Variant Hirschsprung's disease. J Pediatic Surg 1997;32:149-157.
2 Li NP, Wu RL, Zhou S. Investigation on the pathological morphology of intestinal neuronal dysplasia. Chin J Pediatr Surg 2000;21:221-222.
3 Zhu XM, Gu ZC, Wang XD. The morphometric study of myenteric plexus of colon in children with hypoganglionosis. Chin J Pediatr Surg 2005;26:536-539.
4 Meier-Ruge WA, Ammann K, Bruder E, Holschneider AM, Schärli AF, Schmittenbecher PP, et al. Updated results on intestinal neuronal dysplasia (IND B). Eur J Pediatric Surg 2004;14:384-391.
5 Feng JX, Shi HF, Wang G. Analysis of the acetylcholinestase activity in rectal suction biopsy of 1008 children with constipation. Chin J Pediatr Surg 2004;25:518-520.
6 Bagdzevicius R, Vaicekauskas V, Bagdzeviciūte S. Experience of acetylcholinesterase histochemistry application in the diagnosis of chronic constipation in children. Medicina (Kaunas) 2007;43:376-384.
7 Yi B, Wang XL, Wei MF. Anorectal manometry and pathologic analysis of children with intestinal neurodysplasia. J Appl Clin Pediatr 2005;20:809-811.
8 Wang G, Sun XY, Wei MF, Weng YZ. Heart-shaped anastomosis for Hirschsprung's disease: Operative

technique and long-term follow-up. World J Gastroenterol 2005;11:296-298.
9 Bentley JF. Some new observations on magacolon in infancy and childhood with special reference management of megasigmoid and megarectum. Dis Colon Rectum 1964;7:462-470.
10 Kobayashi H, Yamataka A, Lane GJ, Miyano T. Pathophysiology of hypoganglionosis. J Pediatr Gastroenterol Nutr 2002;34:231-235.
11 Holschneider AM, Meier-Ruge W, Ure BM. Hirschsprung's disease and allied disorders—a review. Eur J Pediatr Surg 1994;4:260-266.
12 Kubota A, Yamauchi K, Yonekura T, Kosumi T, Oyanagi H, Mushiake S, et al. Clinicopathologic relationship of hypoganglionosis. J Pediatr Surg 2001;36:898-900.
13 Meier-Ruge WA, Brunner LA, Engert J, Heminghaus M, Holschneider AM, Jordan P, et al. A correlative morphometric and clinical investigation of hypoganglionosis of the colon in children. Eur J Pediatr Surg 1999;9:67-74.
14 Shi CR, Chen QM, Pan WH. Clinical and pathologic characteristics of neuronal intestinal disorder. J Surg Concepts Pract 2000;5:181-184.
15 Taguchi T, Masumoto K, Ieiri S, Nakatsuji T, Akiyoshi J. New classification of hypoganglionosis: congenital and acquired hypoganglionosis. J Pediatr Surg 2006;41:2046-2051.
16 Wedel T, Roblick UJ, Ott V, Eggers R, Schiedeck TH, Krammer HJ, et al. Oligoneuronal hypoganglionosis in patients with idiopathic slow-transit constipation. Dis Colon Rectum 2001;45:54-62.
17 Feng JX, Li MJ, Gu WZ, Tang HF. Diagnosis and surgical treatment of neuronal intestinal dysplasia type B in childhood. Chin J Gen Surg 2003;18:350-352.
18 Hayakawa K, Hamanaka Y, Suzuki M, Nakatsu M, Nishimura K, Tanaka M, et al. Radiological findings in total colon aganglionosis and allied disorders. Radiat Med 2003;21:128-134.
19 Martucciello G, Pini Prato A, Puri P, Holschneider AM, Meier-Ruge W, Jasonni V, et al. Controversies concerning diagnostic guidelines for anomalies of the enteric nervous system: a report from the fourth International Symposium on Hirschsprung's disease and related neurocristopathies. J Pediatr Surg 2005;40:1527-1531.
20 Kobayashi H, Li Z, Yamataka A, Lane GJ, Miyano T. Overexpression of neural cell adhesion molecule (NCAM) antigens on intestinal smooth muscles in hypoganglionosis: is hypoganglionosis a disorder of the neuromuscular junction? Pediatr Surg Int 2003;19:190-193.
21 Inoue K, Shimotake T, Tomiyama H, Iwai N. Mutational analysis of the RET and GDNF gene in children with hypoganglionosis. Eur J Pediatr Surg 2001;11:120-123.
22 Rolle U, Yoneda A, Solari V, Nemeth L, Puri P. Abnormalities of C-Kit-positive cellular network in isolated hypoganglionosis. J Pediatr Surg 2002;37:709-714.
23 Yamataka A, Fujiwara T, Nishiye H, Sunagawa M, Miyano T. Localization of intestinal pacemaker cells and synapses in the muscle layers of a patient with colonic hypoganglionosis. J Pediatr Surg 1996;31:584-587.

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