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Hirschsprung's disease and intestinal neuronal dysplasia – a frequent association with implications for the postoperative course

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Abstract Between 1991 and 1993, 106 newly diagnosed cases of Hirschsprung's disease (HD) were prospectively analyzed for the association of HD and intestinal neuronal dysplasia (IND) at ten pediatric surgical departments in central Europe. Hirschsprung-associated IND (HaIND) was found in 40% of cases. IND was disseminated in one-third and localized in two-thirds of the patients. Initial clinical symptoms were related to the length of the aganglionic segment, but not to the presence of HaIND. An enterostomy performed in 72 cases (67.9%) was located in a segment of pathologically innervated bowel in 50% of all cases, but in 72% of cases of HaIND. The proximal margin of the resected bowel showed pathological innervation in 44% of cases. Supplemental biopsies from the intestine (apart from diagnostic suction biopsies and biopsies at the enterostomy site) led to the first identification or definition of length of associated IND in 17.9% of cases. Postoperatively, the presence of long-segment aganglionosis or associated IND implied a delay in the restoration of normal defecation. Persistent constipation was found in 40% of patients with associated *disseminated* IND at follow-up at 6 months, compared to 20.6% in patients with isolated HD. These children needed secondary interventions more often than patients with associated localized IND or isolated HD. HaIND thus has clinical implications for the postoperative course if IND is disseminated.

Key words Hirschsprung's disease · Intestinal neuronal dysplasia · Hirschsprung-associated intestinal neuronal dysplasia · Pull-through operation

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Introduction

The diagnosis and therapy of Hirschsprung's disease (HD) are well-standardized. Relying on electromanometry, radiologic (contrast enema), and biopsy findings, resection is performed according to four established surgical procedures with or without a temporary enterostomy [14]. Newer scientific perceptions and clinical considerations refer to the etiology and pathogenesis, the significance of malformations of non-adrenergic, non-cholinergic innervation, and technical modifications like stapler anastomosis, laparoscopy, or primary pull-through procedures in the newborn [24, 25, 28].

Persistent constipation is the most important long-term problem in patients operated for HD unrelated to any specific surgical procedure. Holschneider reported constipation in 7.9% to 10.4% of patients [6], and more recent publications show similar results [5, 12]. Inade-

quate resection, anastomotic stricture, or achalasia of the internal anal sphincter have been suggested as causes of this sequela [7]. Anomalies of the innervation of the remaining proximal colonic segment have been discussed in this context. Generally, there is a hypoganglionic transitional zone at the cranial end of the aganglionic segment. In 1973, Lassmann and Wurnig were the first to describe two patients with a hyperganglionic segment proximal to the aganglionic bowel [10]. Hyperganglionosis was later called intestinal neuronal dysplasia (IND). This observation has been confirmed by several case reports and retrospective evaluations. The ratio of HD-associated IND (HaIND) has been reported as 10.4% to 78.6%, with a total of 174 patients reported in the literature up to 1994 [4]. A reliable incidence of HaIND has not been determined, however, and its clinical significance is debated. The cranial extent of the dysganglionic segment has been evaluated only in single cases, differentiating the localized and disseminated forms of HaIND. Therefore, evidence-based data for predicting therapeutic consequences in HaIND are still lacking. The aim of this prospective, multicenter study was to evaluate the ratio and forms of HaIND and to analyze the incidence of postoperative complications.

Materials and methods

From 1991 to 1993, ten pediatric surgery departments in Germany, Austria, and Switzerland (Table 1) prospectively documented all newly-diagnosed patients with aganglionosis. HD and IND were evaluated by rectal suction biopsies as well as specimens from any enterostomy, resected bowel, specimen at enterostomy closure, or any further intervention (Fig. 1). Because of the risks of intestinal biopsy (perforation, leakage), the number, localization, and type of biopsies (full-thickness or extramucosal) were decided based on the individual need to define the margin of disturbed innervation. In general, the presence of HaIND did not influence the extent of resection.

A five-part questionnaire was filled in for every patient. The *first part* adressed the case history and results of diagnostic procedures (X-ray, biopsies) and treatment modalities (initial enterostomy or primary resection). The *second* referred to the enterostomy if performed, its position, and any further diagnostic measures done afterward. The *third part* registered the definitive surgical procedure as well as methods and results of the histologic work-up, comprising native tissue work-up, cryostat sections of 15 μm thickness, and examination of 20–40 consecutive sections stained with acetylcholinesterase (AChE) and lactate or succininic dehydrogenase reactions. This documentation included the length of the aganglionic segment, HaIND if present, and extent of the IND. The dysganglionic segment was evaluated as localized, i.e., a limited intestinal segment with normal innervation at the cranial end, or disseminated, i.e., all biopsies including large parts of the small bowel showed IND. The *fourth part* covered the postoperative course: surgical complications and clinical course. In the *fifth* weight gain, nutrition, medications if any, and defecation behavior were noted at follow-up 6 months postoperatively.

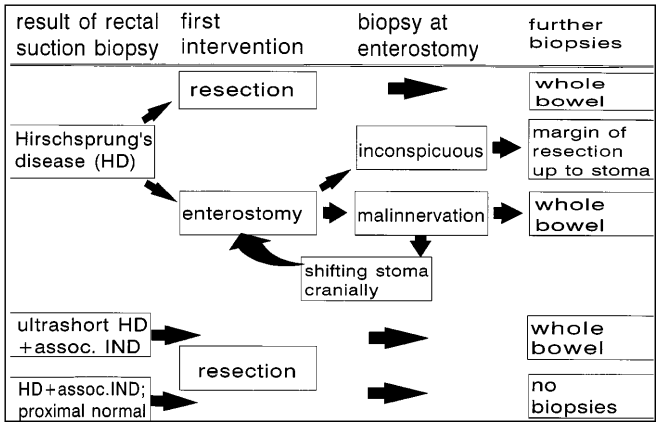

Fig. 1 Evaluation of associated IND

Table 1 Participants in the study and numbers of patients (*D* Germany, *A* Austria, *CH* Switzerland)

Department of Pediatric Surgery	Head of the department at time of study and responsible co-worker	Number of patients
Benjamin Franklin University, Berlin, D	J. Waldschmidt D. Cholewa	13
University Children's Hospital, Graz, A	H. Sauer A. Haberlik	7
University Hospital, Hannover, D	H. Mildenberger L. Meyer-Junghänel	7
University Hospital, Innsbruck, A	G. Menardi	14
Municipal Hospital, Karlsruhe, D	W. Brands W. Schuppert	9
Children's Hospital "Park Schönfeld", Kassel, D	E. Heiming J. Moczulski	7
Municipal Children's Hospital, Köln, D	A. Holschneider B. Ure	19
Children's Hospital, Luzern, CH	A.F. Schärli E. Rumlova	6
University Children's Hospital, München, D	I. Joppich P.P. Schmittenbecher	19
University Children's Hospital, Zürich, CH	U. Stauffer P. Sacher	5
Total		106

All data were transferred to a databank (PARADOX, Borland, Munich). For statistical evaluation, the data were analyzed by STAT VIEW TM II R (Abacus Concepts, 1987/1991). Single parameters were calculated by the chi square test for unpaired populations and statistical significance was defined as P less than 0.05.

Results

Data from 106 patients were collected from six university departments and four municipal or private institutions (Table 1). Nine children were diagnosed as having Down's syndrome (8.5%). The extent of aganglionosis and the proportion of cases with HaIND are shown in Table 2 and Fig. 2. HaIND was found in 40% of all cases; IND was localized in about two-thirds and disseminated in one-third. There was no significant difference regarding HaIND in ultrashort and "typical" rectosigmoid cases of HD (39.7%) compared to long-segment aganglionosis (40.7%). In short-segment cases, the disseminated form of IND was found more often than in long-segment cases (1.4:1 vs 4.5:1), but this did not reach statistical significance ($P = 0.2954$).

HaIND did not significantly influence the initial clinical presentation or the need for early emergency intervention. Ileus was found in 21.4% of cases with HaIND and 11.1% with isolated HD ($P = 0.1387$). This occurrence was more related to the length of the aganglionic segment ($P = 0.0786$). Barium enemas did not show any specific findings in HaIND. The diagnosis of aganglionosis relied on rectal suction biopsies in 96 patients (90.6%) and on distinct clinical and/or radiologic signs of HD in 10 (9.4%). The most proximal rectal biopsy showed normal innervation in 10 cases, was hypoganglionic in 1, and showed IND in 6. In 79 cases (74.6%) all rectal biopsies were aganglionic. Seventy-two children (67.9%) underwent placement of an enterostomy. In 10 newborns, a primary enterostomy was performed without prior biopsies due to distinct clinical or radiologic signs of HD. In 33 patients (31.1%) a primary resection was performed. One patient died before definitive surgery.

Table 2 Extent of aganglionosis

Extent of aganglionosis	Number of patients	%
Ultrashort	6	5.7
Rectosigmoid	72	68.6
Long-segment colonic	21	20
Total colonic	2	1.9
Small-bowel involvement	4	3.8

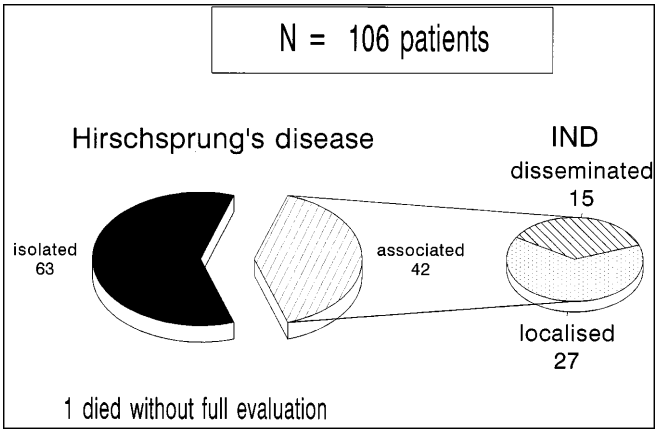

Fig. 2 Incidence of Hirschsprung-associated IND

Decisions for therapy were made according to the local routine procedure, unrelated to the presence or absence of HaIND. Table 3 summarizes the localization and histologic evaluation of the enterostomies. Only in 50% of cases was the enterostomy located in a normally-innervated bowel segment, 75% of isolated HD and 28% of HaIND cases ($P = 0.0003$). A bowel resection was performed using the Rehbein method in 89 cases (84%), the Duhamel method in 5 (4.7%), the Soave procedure in 3 (2.8%), and the Swenson operation in 1 (1%). A sphincteromyectomy was performed in 3 cases and Hartmann's operation once. In 3 patients the method was not described and 1 child died before definitive surgery was undertaken. Enterostomies were closed at the time of resection (22 patients) or after verified healing of the anastomosis (45 patients), independent of the type of innervation at the enterostomy site. Five enterostomies were replaced in a more proximal bowel segment and closed later.

Methods of morphologic evaluation were documented in 86 cases. The AChE reaction was used in 83 patients and one or two additional dehydrogenase reactions in 60. Different supplemental investigations were performed, i.e., the S 100 reaction (20), NADPH (13), neuron-specific enolase (6), and others (4). In 10 cases AChE was used exclusively. The histologic findings of resected intestinal specimens are shown in Table 4. The histologic work-up revealed abnormal intestinal inner-

Table 3 Position of enterostomy and results of morphologic evaluation

Position of enterostomy	Morphologic evaluation	Consequence
Sigmoid $N = 2$	1 × aganglionosis 1 × dysganglionosis	no
Left flexure $N = 3$	2 × aganglionosis 1 × hypoganglionosis	no
Transverse colon $N = 56$	32 × normal 3 × aganglionosis 4 × hypoganglionosis 16 × dysganglionosis 1 × no evaluation	2 × enterostomy replaced more cranially
Right flexure $N = 5$	3 × normal 1 × dysganglionosis 1 × no evaluation	2 × enterostomy replaced more cranially
Ileum/jejunum $N = 6$	1 × normal 2 × aganglionosis 2 × dysganglionosis 1 × no evaluation	1 × enterostomy replaced more cranially

Table 4 Results of morphologic evaluation of resected segments (*IND* intestinal neuronal dysplasia)

Main innervational finding of resected bowel segment	Morphology of cranial resection border	No. of patients
Normal ganglia	Normal innervation	2
Hypoganglionic segment	Normal innervation	5
Aganglionosis	Normal innervation	45
Aganglionosis and IND	Normal innervation	4
Aganglionosis	Hypoganglionic segment	2
Aganglionosis	IND	32
Aganglionosis	Persistent aganglionosis	10
Histologic expertise not given		5

vation at the cranial end of the resected bowel in 44 patients (44% of the 100 submitted findings), 11 (18.3%) with isolated HD and 33 (82.5%) with HaIND ($P = 0.0001$). Cranial to the proximal margin of resection, 235 biopsies were taken in 92 patients (87.7%) in order to newly identify or evaluate the extent of IND if present (Table 5). In 13 children (12.3%) the proximal limit of abnormal innervation was defined by suction biopsies or biopsies from the enterostomy and no further biopsies were necessary. In 3 (2.8%), HaIND was first diagnosed by these additional biopsies. In 16 children (15.1%) determining the IND level and differentiation between the localized and disseminated forms was possible.Therefore, in 17.9% of all patients supplemental information was gathered by means of additional biopsies.

Five children died (4.7%), 3 in the postoperative period due to perforation, sepsis, and toxic megacolon, 1 of unknown causes with an ileostomy in situ, and 1 due to cardiac decompensation. Altogether, 13 patients (12.3%) – 9 with HD and 4 with HaIND – had 17 complications. Those were localized (abscess, anastomotic leak, stenosis, neurogenic bladder) in 6 and systemic (ileus, enterocolitis, perforation, sepsis, thrombopenia) in 11. In 48 children (45.3%), 25 with HD and 23 with HaIND, bouginage of the anastomosis was necessary. None of these occurrences was significantly influenced by HaIND. The onset of spontaneous postoperative bowel movements was significantly delayed in patients with long-segment aganglionosis ($P = 0.0049$) and those with HaIND ($P = 0.0257$). The start and completion of enteral nutrition was delayed in patients with long-segment aganglionosis ($P = 0.0057$ and 0.0239, respectively), but not with HaIND ($P = 0.4431$ and 0.4387, respectively).

At 6-month follow-up, 13 children (12.3%; 9 HD and 4 HaIND) showed insufficient weight gain, 22 (20.8%; 13 HD and 9 HaIND) had constipation, and 13 (12.3%; 7 HD and 6 HaIND) had diarrhea, all without accentuation of the HaIND. In 25 children 32 secondary interventions were needed (23.6%; $P = 0.551$; 15 HD and 10 HaIND). Table 6 summarizes the measures taken in the children with impaired defecation at follow-up. Disseminated HaIND was present in 40% of cases ($P = 0.1767$); all of these patients needed at least one additional intervention.

Table 5 Number, localization, and histologic findings in biopsies proximal to cranial border of resection

	Descending colon	Transverse colon	Ascending colon	Ileum	Jejunum
Biopsy avoided	25	31	68	81	90
Biopsy done	81	75	38	25	16
Normal	34	40	18	11	8
Dysganglionic	16	23	13	9	6
Hypoganglionic	3	2	0	2	1
Aganglionic	28	10	7	3	1

Table 6 Secondary interventions at 6-month follow-up (*HD* Hirschsprung's disease, *IND* intestinal neuronal dysplasia)

Measures	No. of patients	Isolated HD	Localized IND	Disseminated IND
Secondary enterostomy	11	8	2	1
Secondary sphincteromyectomy	6	2	2	2
Secondary resection	3	3	–	–
Long-term bouginage/sphincter dilatation	11	8	–	3
Total parenteral nutrition	1	1	–	–

Discussion

Approximately 10% of patients with HD have prolonged constipation postoperatively [6, 7]. The presence of ganglion cells at the cranial end of the resected specimen does not guarantee sufficient function of the remaining colon. Deficits of neuromuscular connections, abnormal distribution of peptidergic nerves, increased mesenchymal substances (laminin or collagen IV), and reduced synthesis of RET protein have been described in the remaining colon [11, 18, 22, 29] and may be the cause of postoperative constipation.

Lassmann and Wurnig [10], Puri et al. [21], and Gulotta and Straaten [2] were among the first to report HaIND. Meier-Ruge found IND in 34.4% of patients with HD in his specialized laboratory [13]. Meanwhile, the existence and relevance of associated IND is generally accepted even by groups with initial doubts about this entity [8, 21]. However, most studies were retrospective, and no data were given as to the length of the segments affected with IND. The present prospective study showed HaIND in 40% of all patients; only the registration of each case of IND will enable the correct estimation of this finding to be determined.

No significant difference was found in the preoperative clinical course of patients with isolated HD compared to patients with HaIND, and HaIND did not significantly influence the need for early emergency intervention. Interestingly, the occurrence of ileus was most closely related to the length of the aganglionic segment. Radiologic evaluations did not reveal any specific pattern of IND.

An enterostomy, if performed, was placed in the transverse colon in most cases. Normal innervation at the enterostomy site was found only in isolated HD. The enterostomies in HaIND were located in colonic segments with pathological innervation in 72% of cases in the present series. Nevertheless, these colostomies all functioned well. The adequate function of these colostomies may represent passive emptying of the colon, and does not prove sufficient contractility of the remaining colon to pass stools through the aganglionic sphincter and remaining rectum after pull-through, however [19, 20].

The method of intestinal resection is of utmost interest. It has been suggested that a Soave or Duhamel pull-through may be of advantage in HaIND because the limited or poor peristalsis might not be blocked by a circular anastomosis and the aganglionic rectal stump. In the present series the Rehbein method was used in the majority of patients (84%), and therefore, a comparison with other methods is not possible.

Postoperatively, there was a delay of regular defecation in the patients with HaIND. Fadda et al. [1] reported motility disorders in one-third of children with HaIND and Kobayashi et al. [8] found defecation disorders in all of their patients with HaIND. Hanimann et al. [3] described constipation in the early postoperative course in 18.2% of their patients with HaIND and 8.3% with isolated HD. All of their patients underwent a Duhamel procedure, without total resection of the IND segment if one was found.

The present study revealed a constipation rate of 20.8% at 6-month follow-up; 40% of the children with disseminated HaIND were affected. These children required long-term bouginage and other secondary interventions such as sphincteromyectomy or redo of an enterostomy more often than children with isolated HD or localized HaIND. Ure et al. [27] reported that a secondary resection was necessary significantly more often in patients with HaIND. Moore et al. [16] noted obstructive symptoms in 14%, one-half of them in patients with HaIND.

Morphologic mapping during the initial operation has been recommended [8, 15]. A search for dysganglionosis seems to be indispensable at the latest when early and severe obstructive symptoms occur after intestinal resection. Surgeons favoring placement of an enterostomy may take advantage of initially performing this mapping by biopsies. A full-thickness biopsy from the enterostomy site should be taken in any case to evaluate the pattern of innervation there.

According to Fadda et al. [1], the goals of therapy in patients with HaIND are to resect the aganglionic segment and at the same time to handle the dysganglionic part according to its function. In cases of proven HaIND, these authors recommend performing an enterostomy and postponing the resection for at least 1.5 to 3 years. Depending on the motility, they decide on an extended resection. Pistor et al. [20] checked motility by functional colonic ultrasound (US) and decided on the extent of resection based on US findings that might show maturation of function. However, this procedure was never proven useful under standardized conditions. Morphologic controls by Munakata et al. [17] did not show any clear correlation between histomorphology and function.

In the absence of a standardized therapeutic plan one can only refer to successful procedures of single institutions. Koltai [9] suggests performing a valve-like intestinal fistula in HaIND that closes spontaneously if intestinal passage is undisturbed. Ure et al. [26] proposed resecting approximately one-third of the dysganglionic segment, and Schärli [23] suggested limited resection of segments with definite abnormal motility.

In conclusion, this prospective study showed that aganglionosis was associated with IND in 40% of patients, the disseminated form of IND in one-third and the localized form in two-thirds. Biopsy mapping led to additional information in 17.9% of cases, showing the presence and length of any IND segment. The enterostomy site showed patterns of irregular innervation in 72% of patients with HaIND, but no impairment of function of the colostomies was noted. Patients with HaIND mainly operated upon by the Rehbein method show delayed restoration of defecation postoperatively. Children with the disseminated form of HaIND had a

higher rate of postoperative constipation at follow-up, and all of them needed secondary interventions. Histomorphologic mapping prior to resection may be helpful to design an individualized therapeutic plan. Further studies are necessary to evaluate the extent, timing, and preferred method of resection in cases of HaIND, and data on morphologic and functional maturation will have to be evaluated in the future.

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