Clinical Aspects of Intestinal Neuronal Dysplasia

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Purpose: The aim of this study was to determine the presence of specific clinical symptoms in intestinal neuronal dysplasia (IND) and whether it correlates to the severity of histopathologic findings.

Methods: A group of 44 severe IND and a group of 16 mild IND patients diagnosed by means of a histochemical rectal biopsy were compared with a group of 37 patients with functional constipation (FC) with normal rectal biopsy results.

Results: Patients with severe IND began their symptoms at an earlier age than those with mild IND and FC (5.2 ± 112 months *v* 17.5 ± 23 months and 22.5 ± 21.8 months, respectively; $P < .001$). The presence of intestinal obstruction symptoms was more frequent in severe IND patients than in mild IND and FC patients (45.5% *v* 18.8% *v* 2.7%, respectively; $P < .001$). The presence of a fecaloma and soiling were less frequent in the severe IND group than in mild IND and FC groups (20.5% *v* 56.3% *v* 59.5%, respectively; $P < .001$ and 15.9% *v* 31.3% *v* 59.5%, respectively; $P < .001$). Barium enema results showed a lower incidence of rectosigmoid distension in severe IND if compared with mild IND and FC groups (45.5% *v* 57.1% *v* 96.9%; $P < .001$). Internal sphincter relaxation was absent frequently in the severe IND group compared with the FC group (47% *v* 26.9%, respectively; $P < .05$).

Conclusions: Intestinal neuronal dysplasia is a distinct histopathologic and clinical entity. Its clinical, radiologic, and manometric presentation correlates to the severity of histochemical findings.

INDEX WORDS: Intestinal neuronal dysplasia, constipation, histochemistry, anorectal manometry, congenital malformations.

INTESTINAL NEURONAL DYSPLASIA (IND) was first described by Meier-Ruge in 1971 as a malformation of the enteric plexus of unknown pathogenesis, associated with obstruction of the lower intestine.[1] Since then, its histologic diagnostic criteria have been a matter of controversy. Currently, there is major consensus about IND diagnosis that is based principally on hyperplasia of the submucous plexus with giant ganglia containing more than seven nerve cells, increased acetylcholinesterase activity in the lamina propria and around the submucosal blood vessels, and heterotopic ganglia in the lamina propria.[2,3]

In Hirschsprung's disease, patients have better bowel function after surgical treatment in the isolated forms of aganglionosis than in combined aganglionosis IND forms, suggesting that IND could be the possible cause of persistent symptoms.[4-6] However, although isolated IND has been recognized as a histopathologic entity, many investigators question whether it is a real disease[7,8] and proper investigations about the correlation between the histologic findings and clinical symptoms are lacking.

In our institution, we have studied histochemical intestinal biopsies since 1977, and we have discovered that there is a wide range of histochemical alterations in IND, from slight to severe hyperplasia of submucous plexus.

The aim of our study was to determine the presence of specific clinical, radiologic, and manometric findings in patients with IND and whether they correlate with the severity of histopathologic findings.

MATERIALS AND METHODS

From 1977 to 2001, 651 patients with persistent chronic constipation underwent surgical rectal biopsy, including enough mucosa and submucosa, taken from 2 cm above the pectinate line. The specimens were stained for acetylcholinesterase and succinic dehydrogenase reaction. All the biopsy results were studied by the senior author. We do not routinely use sympathetic innervation staining, so we have not been able to diagnose any IND type A. This study includes only isolated IND type B.

In our institution, we have classified IND according to the severity of histochemical alterations into 2 groups: mild IND and severe IND. The criteria used for the diagnosis of severe IND include hyperplasia of the submucous plexus, giant ganglia with more than 7 nerve cells, increased acetylcholinesterase activity in the lamina propria or surrounding submucosal blood vessels, and heterotopic neuronal cells in the lamina propria. Any biopsy that showed giant ganglia of the submucous plexus with only one of the other elements was considered mild IND.

Among the 651 patients investigated, we found 356 (54.7%) normal

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Table 1. Symptoms and Findings on Barium Enema

	Functional Constipation (n = 37)	Mild IND (n = 16)	Severe IND (n = 44)	*P* Value (Among 3 Groups)
Gender: M/F	22/15	12/4	20/24	Not significant
Age (mo; mean ± SD)	22.5 ± 21.8	17.5 ± 23	5.2 ± 112	<.001
Intestinal obstruction (%)	1 (2.7)	3 (18.8)	20 (45.5)	<.001
Fecaloma (%)	22 (59.5)	9 (56.3)	9 (20.5)	<.001
Soiling (%)	22 (59.5)	5 (31.3)	7 (15.9)	<.001
Rectosigmoid distension (%)	31/32 (96.9)	8/14 (57.1)	15/33 (45.5)	<.001

biopsy results; 104 (15.9%) aganglionosis; 83 (12.7%) cases of isolated severe IND, 31 (4.8%) cases of isolated mild IND, and 12 (1,8%) cases of hypoganglionosis. In 65 (9.9%) biopsies, the defect was not classifiable.

Because we have been performing anorectal manometries since 1995, patients without this diagnostic procedure were ruled out of this study. We reviewed retrospectively 16 medical records of mild IND patients and 44 of severe IND patients. As a control group we used 37 patients with chronic constipation with normal rectal biopsy results. No patient in this group had any secondary disease that could cause constipation, so it was named *functional constipation (FC) group*. We compared these 3 groups according to their clinical symptoms, findings on barium enema, internal sphincter relaxation, and anorectal compliance in anorectal manometry. Local Ethics Committee approval was obtained for this study. Analysis of variance (ANOVA) and Kruskal-Wallis tests were used for statistical analysis of the results, where $P < .05$ was considered significant.

RESULTS

There were no differences in sex distribution among these 3 groups. The median age of presentation for severe IND group was 5 months, ranging from 1 month to 10 years, which was significantly lower than the mild IND group (17 months). The latter occurred at an earlier age than the FC group (22 months; Table 1). All patients showed different degrees of chronic constipation ranging from slight constipation to severe cases with abdominal distension and vomiting. The presence of signs and symptoms of intestinal obstruction were found more frequently in severe IND patients (45.5%) than in the mild IND group (18.8%). There was only one patient with a normal biopsy result who had abdominal distension in the newborn period (Table 1). By contrast, fecaloma and soiling were more frequently present in FC patients (59.5% for both) than in mild IND patients (56.3% and 31.3%, respectively). The severe IND group had the lowest rate of fecaloma and soiling (20.5% and 15.9%, respectively; Table 1).

Barium enema was performed in 32 of 37 patients of the FC group; in 8 of 14 of the mild IND group and in 15 of 33 of the severe IND group. We found different degrees of rectosigmoid distension in all groups in almost all FC patients (96.9%); however, it was less frequent in the mild IND group (57.1%). Severe IND patients had the lowest incidence of rectosigmoid distension on barium enema (45.5%; Table 1). There was no other specific radiologic alteration besides rectosigmoid distension in any group.

Anorectal manometry was performed in 26 of 37 FC patients; in 6 of 16 mild IND patients, and in 17 of 44 severe IND patients. Internal sphincter relaxation was either present or absent or atypical in all 3 groups of patients. We found a significantly higher rate of absence of internal sphincter relaxation in the severe IND group (47.1%) than in the FC group (26.9%; Table 2). The median anorectal compliance value was higher in the FC group (10 mL/mm Hg) than in both the mild IND and the severe IND groups (1.4 and 2.2 mL/mm Hg, respectively) although it did not reach statistical significance (Table 2).

Congenital malformations associated with IND are listed in Table 3. We encountered 25% of associated anomalies in mild IND patients and 34% in severe-IND patients (not statistically significant). The overall incidence of anorectal malformations for both groups was 20%.

DISCUSSION

There is a wide spectrum of histologic alterations in IND, ranging from slight to severe forms. For this reason, its diagnostic criteria has been a matter of discussion among different investigators for years, and the incidence of IND has varied considerably among different

Table 2. Anorectal Manometry

	Functional Constipation (n = 37)	Mild IND (n = 16)	Severe IND (n = 44)	*P* Value
Internal sphincter relaxation				
Present (%)	16/26 (61.5)*	4/6 (66.7)	4/17 (23.5)*	<.05
Absent (%)	7/26 (26.9)*	2/6 (33.3)	8/17 (47.1)*	<.05
Atypical (%)	3/26 (11.5)*	—	5/17 (29.4)*	<.05
Anorectal compliance (mL/mm Hg; mean ± SD)	10 ± 9.9	1.4 ± 0.8	2.2 ± 2.2	Not significant

**P* value among these groups.

Table 3. Associated Malformations in Intestinal Neuronal Dysplasia

	Mild IND (n = 16)	Severe IND (n = 44)
Anal stenosis	2	7
Rectoperineal fistula	—	1
Rectourethral fistula	—	1
Left colon stenosis	—	1
Ventricular septal defect	—	2
Truncus arteriosus	—	1
Pelviureteric junction obstruction	1	1
Down syndrome	—	1
Sensorineural deafness	1	—
Total	4/16 (25%)	15/44 (34%)

countries.[3,4,9,10,11] According to our results, symptoms and examination findings are not pathognomonic in IND, and many of them overlap with FC findings. However, our findings clearly show that some of them are more characteristically present in IND patients leading to a specific clinical pattern, different from functional constipation. Our classification of IND into 2 severity groups was helpful in showing a clear clinicopathologic correlation.

The incidence of IND in our series was 17.5%, which is similar to previous findings by other investigators.[9] Nevertheless, because there are different criteria in rectal biopsy indications, it is not proper to compare IND's percentages between series.

According to our results, the characteristic clinical pattern of IND can be found in less than one-year-old infants with a history of constipation and abdominal distension, thus, mimicking Hirschsprung's disease, with absence of internal sphincter relaxation in anorectal manometry but who have a normal barium enema. The median age on presentation of severe IND was 5 months, and similar results have been reported in other series.[3] Intestinal obstruction is the most characteristic clinical symptom of IND. However, fecaloma and soiling are most characteristically found in patients with functional constipation. Although many cases of IND are clinically indistinguishable from Hirschsprung's disease, barium enema findings in IND often are equivocal or show slight to moderate rectosigmoid distension, but lack the typical narrow segment of aganglionosis.[12] The high incidence of rectosigmoid dilatation on barium enema and the value of anorectal compliance in the FC group are related. Although the internal sphincter relaxation was frequently absent in anorectal manometry in severe IND patients, there is not a pathognomonic pattern of the relaxation reflex, and this can be either atypical or normal.[13]

We found a high incidence of associated anomalies in IND patients, and most of them are anorectal malformations, suggesting a relationship between the development of the hindgut and of the enteric nervous system.[14]

IND has been a controversial topic since its first description. Our results show that there are clinical symptoms and examination findings supporting its histologic appearance, resulting not only in a histopathologic but also a distinct clinical entity.

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