Intestinal neuronal dysplasia type B: A still little known diagnosis for organic causes of intestinal chronic constipation

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Intestinal neuronal dysplasia type B (IND-B) is a controversial entity among the gastrointestinal neuromuscular disorders. It may occur alone or associated with other neuropathies, such as Hirschsprung's disease (HD). Chronic constipation is the most common clinical manifestation of patients. IND-B primarily affects young children and mimics HD, but has its own histopathologic features characterized mainly by hyperplasia of the submucosal nerve plexus. Thus, IND-B should be included in the differential diagnoses of organic causes of constipation. In recent years, an increasing number of cases of IND-B in adults have also been described, some presenting severe constipation since childhood and others with the onset of symptoms at adulthood. Despite the intense scientific research in the last decades, there are still knowledge gaps regarding definition, pathogenesis, diagnostic criteria and therapeutic possibilities for IND-B. However, in medical practice, we continue to encounter patients with severe constipation or intestinal obstruction who undergo to diagnostic investigation for HD and their rectal biopsies present hyperganglionosis in the submucosal nerve plexus and other features, consistent with the diagnosis of IND-B. This review critically discusses aspects related to the disease definitions, pathophysiology and genetics, epidemiology distribution, clinical presentation, diagnostic criteria and therapeutic possibilities of this still little-known organic cause of intestinal chronic constipation.

Abstract

Intestinal neuronal dysplasia type B (IND-B) is a controversial entity among the gastrointestinal neuromuscular disorders. It may occur alone or associated with other neuropathies, such as Hirschsprung's disease (HD). Chronic constipation is the most common clinical manifestation of patients. IND-B primarily affects young children and mimics HD, but has its own histopathologic features characterized mainly by hyperplasia of the submucosal nerve plexus. Thus, IND-B should be included in the differential diagnoses of organic causes of constipation. In recent years, an increasing number of cases of IND-B in adults have also been described, some presenting severe constipation since childhood and others with the onset of symptoms at adulthood. Despite the intense scientific research in the last decades, there are still knowledge gaps regarding definition, pathogenesis, diagnostic criteria and therapeutic possibilities for IND-B. However, in medical practice, we continue to encounter patients with severe constipation or intestinal obstruction who undergo to diagnostic investigation for HD and their rectal biopsies present hyperganglionosis in the submucosal nerve plexus and other features, consistent with the diagnosis of IND-B. This review critically discusses aspects related to the disease definitions, pathophysiology and genetics, epidemiology distribution, clinical presentation, diagnostic criteria and therapeutic possibilities of this still little-known organic cause of intestinal chronic constipation.
Key words: Intestinal neuronal dysplasia type B; Hyperplasia of the submucosal nerve plexus; Intestinal chronic constipation; Gastrointestinal neuromuscular diseases; Dysganglionosis

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Core tip: Intestinal neuronal dysplasia type B (IND-B) is a controversial entity among the gastrointestinal neuromuscular disorders. Chronic constipation is the most common clinical manifestation of patients. IND-B primarily affects young children and mimics Hirschsprung’s disease, but has its own histopathologic features characterized mainly by hyperplasia of the submucosal nerve plexus. Despite the intense scientific research in the last decades, there are still knowledge gaps regarding IND-B. This review critically discusses aspects related to the disease definitions, pathophysiology and genetics, epidemiology distribution, clinical presentation, diagnostic criteria and therapeutic possibilities of this still little-known organic cause of intestinal chronic constipation.

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INTRODUCTION

Intestinal neuronal dysplasia (IND) is a pathological condition that affects the intestinal submucosal nerve plexuses and may occur alone or associated with other neuropathies, such as Hirschsprung’s disease (HD). IND belongs to the group of gastrointestinal neuromuscular diseases and was most recently included in the classification for this heterogeneous group of complex changes in the enteric nervous system.[1,2].

More than 40 years after its original description[3], the pathology of IND remains incompletely elucidated. Commonly, IND is associated with clinical symptoms of intestinal chronic constipation that affect children in their first years of life, similar to those of HD, but IND has its own histopathologic features characterized by hyperplasia of the submucosal nerve plexus[4].

Despite the intense scientific research performed in the last decades which includes more than 250 published scientific articles, there are still gaps in the knowledge on IND’s definition, pathogenesis, diagnostic criteria and therapeutic possibilities[2,5,6].

HISTORICAL ASPECTS

The term IND was first used by Nezelof et al[1] in 1970 to describe three cases of congenital megacolon associated with hyperplasia of the myenteric nerve plexus. One year later, Meier-Ruge presented the first formal description of IND as a condition that is typically associated with low intestinal obstruction and that could resemble HD but with distinctive histopathological features, such as hyperplasia of the submucosal nerve plexuses and increased Acetylcholinesterase activity (AchE) in the parasympathetic nerve fibers in the lamina propria of the mucosa[7].

In 1977, Puri et al[8] described one case of IND associated with HD with rectosigmoid aganglionosis of the nerve plexus and IND in the descending and transverse colon. In 1983, Fadda et al[9] proposed the classification of two clinical and histopathological subtypes of IND: IND type A (IND-A), an extremely rare form, characterized by congenital hypoplasia of the adrenergic enteric nervous system; and IND type B (IND-B), characterized by malformation of the cholinergic submucosal plexus, accounting for more than 95% of all cases. In 1990, a consensus meeting in Frankfurt, Germany, defined the morphological criteria for the diagnosis of IND-B[10]. Since that time, these criteria have been widely used both in clinical practice, follow-up studies and genetic investigations[11-15]. Furthermore, in the 90s, new criteria were proposed that gave greater importance to the need for the identification of giant ganglia in the submucosa for the diagnosis of IND-B[16,17]. In the several published criteria, the giant ganglia are defined by the presence of a minimum number of ganglion cells ranging from 6 to more than 10 per ganglion[16-21].

Given this lack of diagnostic standardization, in 2004, Meier-Ruge et al[5,22] proposed quantitative criteria for the histopathologic diagnosis of IND-B. They defined IND-B by the presence of at least 20% giant nerve ganglia in the submucosa, with more than 8 ganglion cells each, based on the examination of a minimum of 25 submucosal ganglia. Additionally, they used a histochemical panel in frozen sections for the analyses of lactate dehydrogenase, succinyl dehydrogenase and nitric oxide synthase[5,22].

All of these changes in the proposed histopathological criteria for the diagnosis of IND-B have not only caused disparities in its definitions but also skepticism about its existence. The main unsolved problem highlighted in recent publications is if there is a causal relationship between the histological findings and clinical symptoms that would justify the characterization of IND-B as a specific entity[2,4,6,23]. Regarding this situation, the current opinions converge on the need for further research to elucidate the many uncertainties about the clinical and morphological characterization of IND-B[2-4,24].

CLASSIFICATION

Two forms of IND are recognized[9]. IND-A is extremely rare and occurs in less than 5% of all IND cases. Patients with IND-A typically present in the neonatal period with...
symptoms may vary from acute intestinal obstruction to diarrhea with hemorrhagic stools. IND-A is characterized by hypoplasia or aplasia of the adrenergic enteric nervous system. A moderate increase in the acetylcholinesterase activity of the parasympathetic nerves is the reason that such cases are termed IND. In 2005, Meier-Ruge and Bruder considered IND-A to be as a necrotizing enterocolitis caused by immaturity of the sympathetic nervous system of the distal colon. The sympatheic innervation is decreased to different degrees in these patients. The absence of sympathetic synapases within the ganglia of the myenteric plexus and the resultant increase in parasympathetic tone are considered to be responsible for the focal colon spasms. Disorders of blood flow and decreased mucus production seem to be the major factors in the pathogenesis of necrotizing enterocolitis. In the majority of cases, the sympatheic innervation is normal by the eighth month of age. Cases that do not present with this development until 10 mo old may be related to sympathetic aplasia.

In contrast, IND-B represents more than 95% of all cases, which explains why this entity has been more frequently studied in the literature and why many authors consider IND to be a synonym for IND-B. IND-B is characterized by hyperplasia of the parasympathetic submucosal plexuses. Typical histological features of IND-B include hyperganglionosis, giant ganglia, ectopic ganglion cells and increased AChE activity in the lamina propria and around the submucosal blood vessels. The changes associated with IND-B are more common in the distal colon; however, they can affect any segment of the enteric nervous system and occur in different age groups ranging from newborns to adults and alone or in combination with HD. Subtype B can cause severe constipation in childhood, unresponsive to clinical management and can be associated with soiling and hemorrhagic stools, acute bowel obstruction or enterocolitis episodes. Occasionally, IND-B symptoms mimic those of HD, which is its main differential diagnosis. All IND cases associated with HD are of the B subtype.

**Epidemiology**

In 2007, Granero Cendón et al estimated the incidence of IND-B as approximately 1 per 7500 newborns. However, the frequency of IND-B varies widely, and the reported rates range from 0.3% to 40% of all rectal suction biopsies. This wide variation may be attributable to the lack of consensus on the diagnostic criteria. There is also an irregular geographical distribution; the highest rates of diagnosis are in European countries, which can be explained by the fact that the majority of the published research comes from this continent.

The latest published series by Taguchi et al (2014) involved a retrospective multicenter study of cases of IND-B in 167 centers in Japan from 2000 to 2009. These authors reported 13 cases based on standardized morphologic criteria from all of the included centers. However, when the quantitative criteria of Meier-Ruge et al were applied, only 4 of the 13 cases sustained the IND-B diagnosis.

IND proximal to a segment of aganglionosis is not uncommon and has been suggested to be a possible cause of persistent bowel problems after surgery for HD. This association may occur in 6% to 44% of HD patients.

**Genetic Aspects**

Recent studies have addressed the role of genetic and molecular commands in the migration and development of the neuroenteric cells. The proto-oncogene rearranged during transfection (RET) and RET protein act in the migration and proliferation of neuroblasts. Approximately 50% of patients with familial HD present RET proto-oncogenic mutations. This finding highlights the importance of this gene alteration in the pathogenesis of dysganglionosis. Over 20 different mutations have been described in this proto-oncogene, and some of the polymorphisms are associated with particular phenotypes, such as the extension of the aganglionic segment in HD.

Similarly, the existence of a genetic component potentially responsible for IND-B has been investigated. The evidence for this component came from a study of monozygotic twins affected by the disease and reports of families in which several members had the histopathological diagnoses of IND-B over multiple generations. Because IND-B and HD are derived from the enteric nervous system, changes often occur simultaneously in the same patient, and common molecular pathways are likely to be involved in the genes of the two pathological conditions. However, mutations in genes considered to be most relevant to HD, such as RET, glial cell line-derived neurotrophic factor (GDNF), and other selected genes in patients with IND-B, have not yet been identified in patients with IND-B. Only some combinations of single nucleotide polymorphisms in the RET proto-oncogene have been identified in patients with IND-B.

IND-B has been described in some families with other associated congenital anomalies of the gastrointestinal tract, such as intestinal malrotation and multiple endocrine neoplasia type 2. Recently, twins from a Turkish family who presented with IND-B associated with congenital short bowel syndrome were described, which raises the possibility that mutations in the Coxsackie- and adenovirus receptor-like membrane protein (CLMP) gene could be related to IND-B because CLMP is essential for intestinal development, and its expression is related to molecular junctional adhesion.

Different experimental studies in rats and mice have demonstrated that homozygous animals deficient in the NCX/Hox11L1 gene present with megacolon and hyperplasia of the myenteric nerve plexus.
However, Costa et al.(4) (2000) and Fava et al.(53) (2002) failed to demonstrate the presence of mutations or molecular defects in the Hox11L.1 coding region in humans with IND-B.

Another possible genetic mechanism is related to endothelin receptor B(41). One of the endothelin receptors (END3) plays an important role in the development of the enteric nervous system of mice. Holland-Cunz et al.(53) (2003) reported that mice presenting with a heterozygous deficiency in this receptor exhibit histopathological changes similar to IND-B, although they do not exhibit clinical signs of bowel dysmotility. These findings were also not reproducible in human research.

**PATHOGENESIS**

The pathogenesis is also a part of the array of uncertainties regarding IND-B. Several hypotheses have been discussed, although none are widely accepted(6,24).

The histopathological changes that characterize IND-B may come from a genetically primary change that directly influences the embryological development of tissues derived from the neural crest(5). However, these findings have only been identified in experimental studies(14,49-52). This hypothesis is supported by the association with other intestinal and extra-intestinal congenital anomalies(15,54,55).

Another research line conceives IND-B as an adaptive response of the enteric nervous system. IND-B has been considered to be secondary to acquired phenomena caused by congenital obstructions or inflammation occurred during pre-, peri- or post-natal periods in humans(12,13,16,56,57). Morphological findings suggestive of IND-B have been observed in intestinal segments proximal to areas of intestinal atresia, rectal mucosal prolapse and ileostomy, intestinal intussusception, imperforate anus and nercrotizing enterocolitis(58,59,60). This secondary histopathologic response to a bowel obstruction has also been tested in experimental studies with conflicting results(61). Pickard et al.(60) (1981) observed ganglionic hyperplasia in the dilated segment of the proximal jejunum in an experimental model of intestinal atresia in sheep fetuses. The same results were not reproduced by Moore et al.(61) (1993) in a model of partial colon obstruction in adult rats. These authors observed a decrease in the number of ganglion cells in the myenteric nerve plexuses of rats submitted to partial intestinal obstruction. This decrease was explained by an increase in colonic diameter secondary to bowel obstruction(61). The most recent study on this subject was from Gálvez et al.(62) (2004) who identified histopathological changes suggestive of IND-B in some adult rats in a model of chronic colonic obstruction.

An association between IND-B and HD has also been reported(6,35,63-65). In such cases, the segments proximal to the aganglionic obstructed segment present histological characteristics of IND-B(6,54). Thus, these morphological changes of the nerve plexuses of the proximal submucosa segment can be explained both by a primary embryonic modification of the enteric nervous system that could be considered a neurocristopathy that shares a common origin with HD and by a minor change in response to a partial intestinal obstruction(54,63-66).

There is also some evidence that the histopathological changes observed in IND-B can be part of the normal development of the enteric nervous system. As a patient gets older, there is an increase in the size of the ganglion cells and a decrease in their number in the submucosal nerve plexuses(6,22,67-69).

Another conflicting issue is related to whether a cause-effect relationship exists between the histopathological findings of IND-B and the clinical symptoms. In most cases, the diagnosis of IND-B is based on histopathological examinations of rectal biopsies from patients who presented severe constipation(60). However, histopathological changes similar to those of IND-B have been found in the colon of 36 completely asymptomatic children(69). Other studies have failed to demonstrate correlations between the histopathological findings, clinical symptoms, radiological and manometric changes(51,12,47,67). These controversies support the authors who do not consider IND-B as a distinct entity but rather a histopathological alteration of the enteric nervous system that may or may not cause clinical manifestations(6,23,24,64).

**CLINICAL PRESENTATION**

Intestinal chronic constipation has been reported as the commonest clinical presentation in IND-B case series(6,57). In addition to the decrease in bowel movement frequency, the presence of straining at stool, bulky and hardened stools, fecal overflow incontinence and rectal bleeding are usually present as signs and symptoms of chronic constipation(70,71). Therefore, IND-B must be part of the differential diagnosis of possible organic causes for constipation in childhood(72).

In some cases, these symptoms may begin in the first years of life with delays in meconium passage, abdominal distension, vomiting and failure to thrive(73,74). A portion of patients continue to exhibit symptoms throughout life and frequently present with severe constipation unresponsive to several treatment modalities(75-77). These symptoms may improve after 4 years of age, which supports the hypothesis of maturation of the enteric nervous system early in life, since in these cases the histopathological findings of IND-B could disappear concurrently with the symptoms(5).

Severe symptoms, such as enterocolitis episodes, bowel obstruction, volvulus and intussusceptions are rare complications described in different age groups(78-81). In recent years, an increasing number of cases of IND-B in adults have been described(82-86). Some of these cases have exhibited symptoms of severe constipation since childhood(82,83), whereas others experienced the onset of symptoms at adulthood(84). Some patients develop serious complications, such as chronic intestinal pseudo-obstruction, acute bowel obstruction or intestinal infarction(84-86). The oldest reported patient received a
confirmed diagnosis at 71 years of age\(^{(83)}\).

**DIAGNOSIS**

The diagnostic workup used in patients with IND-B must be the same routinely performed during investigation for organic causes of intestinal constipation, particularly focused to exclude HD, which is the most prevalent intestinal dysganglionosis\(^{(6,57,72,87)}\). However, anorectal manometry and barium enema, which are established tests for HD screening, do not present specific results for IND-B\(^{(88,89)}\). Barium enema frequently demonstrate an increased caliber of the rectosigmoid, which is a nonspecific finding typical of patients with constipation, but also may demonstrate conical transition zone, similar to HD\(^{(31,89)}\). Anorectal manometry can reveal absence or presence of an anorectal inhibitory reflex, commonly with atypical morphology, which contributes little to the diagnostic investigation of IND-B\(^{(8,21,89)}\).

Thus, the diagnosis of IND-B essentially relays on histopathological analyses of rectal biopsies\(^{(2,4)}\). The morphological criteria for its diagnosis have changed substantially over the years, leading to difficulties for clinical practice and comparisons between studies. Hyperplasia of the submucosal nerve plexuses is the morphological finding that defines IND-B but that is characterized in different manners according to the adopted criteria\(^{(5)}\). Some authors emphasize the need for the presence of a minimum number of ganglion cells per ganglion or a minimum number of ganglia with these characteristics among the analyzed ganglia for a diagnosis of plexuses hyperplasia\(^{(16,22,72,86)}\) (Figure 1).

Other morphological features, such as the presence of ectopic ganglion cells, increased acetylcholinesterase activity, ganglion cells with a “button” appearance and hypertrophy of the nerve trunks, are considered diagnostic criteria in some studies\(^{(9,10,16,68,79,91)}\).

The criteria described by Meier-Ruge et al\(^{(82)}\) (2004) and slightly altered by Meier-Rouge et al\(^{(9)}\) (2006) suggest a quantitative analysis of the number of ganglion cells in the nervous submucosal plexuses and the identification of at least 20% giant ganglia with at least 8 neurons each, in 25 analyzed nerve ganglia. Frozen 15-μm-thick sections are mandatory and must be subjected to a panel of histochemical tests for lactate dehydrogenase, succinyl dehydrogenase and nitric oxide synthase, and the patient must be older than 1 year of age\(^{(5,22)}\). Although these criteria have been accepted by the scientific community, there are few reports of their use in large series of patients with IND-B\(^{(83)}\). The requirement for fresh frozen sections and the fact that the specific histochemical stainings are not available in most pediatric pathology laboratories are limitations that must be considered. Moreover, it is uncertain whether the numerical criteria applied in these analyses can be applied to 5-μm-thick histological sections embedded in paraffin for standard histological analyses with hematoxylin and eosin or immunohistochemical methods\(^{(22)}\).

**TREATMENT**

Given the numerous uncertainties about the definition, pathogenesis and diagnosis of IND, the lack of consensus regarding its treatment is not surprising. Patients with IND have been subjected to different treatments modalities, that may vary from clinical management, to surgical procedures\(^{(3)}\).

Clinical management includes dietary changes, laxatives and enemas\(^{(16,32)}\). Schimpl et al\(^{(32)}\) (2004) reported satisfactory results in 80% of 105 patients treated with dietary changes, cisapride, laxatives and enemas, in a median follow up period of 7.2 years. Clinical management must follow the currently used guidelines for the treatment of intestinal chronic constipation in children, including fecal desimpaction and laxatives\(^{(72)}\).

Although there is not a well-established role to surgical treatment as in Hirschprung’s disease, there are some reports of this modality of treatment in IND-B\(^{(83)}\). Surgical treatment can be performed through different techniques\(^{(11,46,63,82)}\). Schärli et al\(^{(11)}\) (1992) reported favorable results with a posterior sphincteromyotomy in 13 patients, after a limited 6 mo follow-up period. Some case series with a small number of patients showed symptoms improvement after a temporary colostomy\(^{(6,46,63)}\). Several reports described a colonic resection in patients with
IND-B, commonly performed by an anal pull-through procedure. In most of the cases, there were improvement in the number of bowel movements and in the obstructive symptoms. However, the time of follow-up, the surgical techniques and the length of the resected bowel are quite variable[3,7,9].

The results obtained with these different types of treatment are very discordant. Long-term follow-up studies are lacking and the available studies involve limited numbers of patients[22,32,75]. Thus, the available data nowadays still remains too scarce to establish a therapeutic guideline for IND-B[32,77]. On the other hand, there is a real disease, with its own clinical manifestations and can not be classified only as an histopathological entity[76].

The several types of clinical manifestations directly influence in the treatment. Cases of mild intestinal constipation, without systemic complications or obstructive symptoms, tend to be treated with a conservative clinical management. Most of these cases may resolve spontaneously up to the age of 4 years, due to the maturation of the enteric nervous system[93]. On the other hand, IND-B may present with severe intestinal constipation, with infectious and obstructive symptoms, what require a more invasive treatment[77,91]. Therefore, there is a tendency to consider the conservative choice as a first line therapy in IND-B. The surgical treatment through intestinal resections should be reserved for the cases refractory to at least 6 mo of clinical management, or in the presence of obstructive complications[5,6,31,32,76].

CONCLUSION

IND-B can be considered as a pathological entity characterized by anomalies of the submucous plexus, with a considerable increase in the number of ganglion cells, commonly associated with different degrees of constipation in childhood. IND-B remains surrounded by controversies related to its definition, etiopathogenesis, diagnostic criteria and therapeutic possibilities. However, in medical practice, we continue to encounter children with severe constipation or intestinal obstruction who undergo to diagnostic investigation for HD and rectal biopsies show hyperplastic submucosal ganglia consistent with the diagnosis of IND-B.

In this context, it is of utmost importance to maintain our efforts to clarify the pathophysiology, diagnosis and treatment of this still little-known organic cause of intestinal chronic constipation.

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