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FACULDADE DE MEDICINA

Simone Terra Lourenção

Análise imuno-histoquímica do sistema nervoso entérico na Displasia neuronal intestinal

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutora em Ciências, Área: Patologia.

Orientadora: Profa. Titular Maria Aparecida Marchesan Rodrigues

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"Que minha alma floresça novamente apaixonada por toda a existência."

Rudolf Steiner

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LISTA DE ABREVIATURAS E SIGLAS

AChE	Acetilcolinesterase
Bcl-2	*B-cell lymphoma 2*
CLMP	*Coxsackie and andenovirus receptor-like membrane protein*
DH	Doença de Hirschsprung
DNI	Displasia Neuronal Intestinal
DNI-B	Displasia Neuronal Intestinal Tipo B
GAP43	*Growth Associated Protein 43*
H&E	Hematoxilina e eosina
NCAM	*Neural Cell Adhesion Molecule,* Molécula de adesão celular neural
NGF	*Nerve Growth Factor*
NO sintase	*Nitrous Oxide sintase,* Óxido Nítrico sintase
NSE	*Neuron Specific Enolase,* Enolase neurônio específica
PGP9.5	*Protein Gene Product*, Produto do gene da proteína 9.5
PIP2	Fosfatidilinositol 3,4 bifosfato
PIP3	Fosfatidilinositol 3,4,5 trifosfato
PTEN	*Phosphatase and tensin homologue deleted on chromosome TEN*, Homólogo da fosfatase e tensina deletado no cromossomo dez
SMA	*Smooth Muscle Actin*, Actina de músculo liso

Sumário

SUMÁRIO

Capítulo I

Literature Review

Challenges for the diagnosis of Intestinal Neuronal Dysplasia Type B: a look beyond the number of ganglion cells

1. Introduction

The histopathological diagnosis of colon diseases presenting with chronic constipation in childhood has been a challenge in recent decades. Hirschsprung's disease (HD), considered a study model for other dysganglionoses, shows increased activity of the enzyme acetylcholinesterase (AChE) in the parasympathetic nerves of the lamina propria of the mucosa, the muscularis mucosa, and muscularis propria, due to aganglionosis of the submucosal and myenteric plexuses of the enteric nervous system (ENS). HD and allied disorders include diseases with abnormalities in intestinal ganglion cells or dysganglionosis: (i) immaturity of the enteric nervous system reveals small nerve cells that are difficult to differentiate from glial cells; (ii) hypoganglionosis characterized by 50% reduction in myenteric plexus area and the number of nerve cells; (iii) intestinal neuronal dysplasia type A (a rare form with hypoplasia or adrenergic aplasia) and type B (Muto et al., 2018).

Intestinal neuronal dysplasia type B (IND B) is a controversial entity among gastrointestinal neuromuscular diseases, characterized by complex changes in the ENS, mainly due to hyperplasia of the submucosa nerve plexuses (Meier-Ruge., 2006; Knowles et al., 2010; Friedmacher & Puri, 2013; Schäppi et al., 2013). It was first described in 1970, when Nezelof et al. reported on three cases of megacolon associated with hyperplasia of the myenteric nervous plexuses (Nezelof et al., 1970). A year later, Meier-Ruge defined it as a condition usually associated with low intestinal obstruction that could simulate HD, but which showed distinct histopathological characteristics, such as hyperplasia of the nerve plexuses and increased activity of the

enzyme AChE in the parasympathetic nerve fibers of the lamina propria of the mucosa (Meier-Ruge, 1971).

Almost fifty years have passed and, despite the intense scientific research conducted during this period, there are still countless uncertainties, including its etiopathogenesis, diagnostic criteria, and therapeutic possibilities. Thus, IND B is currently considered a controversial and little-known condition among the differential diagnoses for organic causes of intestinal constipation (Holschneider et al., 2008; Tabbers et al., 2014; Toledo de Arruda Lourenção et al., 2016; Kapur & Reyes-Mugica, 2019).

Most patients with IND B are children with a clinical picture of chronic constipation. Thus, the main symptoms are very similar to those presented by HD patients (Csury & Peña, 1995; Holshneider et al., 2008). Delay in the elimination of meconium, abdominal distention, vomiting and difficulty in eating can appear in the first days of life (Pini-Prato et al., 2007). A portion of these patients can show symptoms throughout their lives, evolving to severe constipation that is refractory to different types of clinical treatment (Schmittenbecher et al., 2000; Gillick et al., 2001; Mattioli et al., 2004). Severe symptoms, such as episodes of enterocolitis, acute intestinal obstruction, volvulus, and intussusception, although rare, are possible complications in different age groups (Sacher et al., 1991; Montedonico et al., 2002; Peng et al., 2011; Jáquez -Quintana et al., 2013). Recent publications have highlighted the growing number of cases in adults, some showing symptoms of constipation since childhood and others with late onset of symptoms (Voderholzer et al., 2000; Vijayaraghavan et al., 2006; López Sanclemente et al., 2014; Junquera Bañares et al., 2014; Vougas et al., 2014). The oldest patient reported in the literature with a diagnosis of IND B was

71 years old. This patient had shown symptoms since childhood, having presented severe constipation for more than 60 years, including several hospitalizations and surgeries during this period (Vougas et al., 2014).

Two therapeutic modalities have been used in patients with IND B: conservative clinical treatment and surgical treatment (Csury & Peña, 1995; Toledo de Arruda Lourenção et al., 2016). Conservative treatment is based on changes in diet, the use of laxatives, and intestinal lavages in cases of fecal retention (Schimpl et al., 2004; Holschneider et al., 2008). Surgical treatment can be performed through sphincterotomy, extensive surgical resection, or temporary colostomy (Briner et al., 1986; Rintala et al., 1989; Schärli, 1992; Tang et al., 2010). However, the outcomes obtained by the different treatment modalities show somewhat conflicting results (Csury & Peña, 1995; Schmittenbecher et al., 2000; Schimpl et al., 2004).

6. Conclusion

Intestinal neuronal dysplasia type B remains a controversial clinicopathological entity, with a poorly understood etiopathogenesis and a series of difficulties related to its diagnosis. Despite these uncertainties, patients continue to present with severe constipation or intestinal obstruction, associated with histopathological alterations compatible with this morphological phenotype, which fully justifies all the effort directed towards new diagnostic perspectives. Only the correct diagnosis of these patients can lead to more effective treatments and better prognosis. In this regard, immunohistochemical techniques have been presented as potential adjuvants for histopathological diagnosis, expanding the horizon beyond counting the number of ganglion cells.

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