The Role of Bcl-2 in Pediatric Functional Bowel Obstruction Cases with Ganglionated Specimens

Thesis

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List of Abbreviations

Abb.	Full term

AChE .....*Acetylcholinestrease*
ADHD.....*Allied Disorders of Hirschsprung's Disease*
Bad .....*Bcl-2–associated death protein*
Bak .....*Bcl-2 homologous antagonist killer*
Bax.....*Bcl-2–associated X protein*
BCL-2 .....*B-cell lymphoma/leukemia-2*
Bcl-xL .....*B-cell lymphoma-extra large*
BH.....*Bcl-2 homology*
Bid .....*BH3-interacting domain death agonist*
BIK .....*BCL2 Interacting Killer*
Bim .....*Bcl-2–interacting mediator of cell death*
BMF .....*Bcl2 Modifying Factor*
BMP.....*Bone morphogenetic proteins*
BMPRIA.....*Bone morphogenetic protein receptor IA*
Caspases .....*Cysteine-aspartic proteases*
CD.....*Cluster of Differentiation*
CLMP .....*Coxsackie and adenovirus receptor-like membrane protein*
CMV.....*Cytomegalovirus*
CNS .....*Central nervous system*
CR.....*Calretinin*
DAB .....*Diaminobenzidine*
DNA.....*Deoxyribonucleic acid*
EDNRB .....*Endothelin Receptor Type B*
ENS .....*Enteric nervous system*
ER.....*Endoplasmic reticulum*
GC.....*Ganglion cell*
GDNF .....*Glial cell-derived neurotrophic factor*
GIT .....*Gastrointestinal tract*
H&E.....*Haematoxylin and Eosin*
HAND2.....*Heart and Neural Crest Derivatives Expressed 2*
HD .....*Hirschsprung's disease*
HG .....*Hypoganglionosis*

List of Abbreviations (Cont...)

Abb.	Full term
HRK	*Harakiri BCL2 Interacting Protein*
IND	*Intestinal Neuronal Dysplasia*
Kg	*Kilogram*
LP	*Lamina propria*
MAP	*Microtubule associated protein*
Mash1	*Mammalian achaete-scute homolog 1*
MBR	*Membrane-bound region*
Mcl-1	*Myeloid cell leukemia 1*
MOMP	*Mitochondrial outer membrane permeabilization*
NADPH-d	*Nicotinamide adenine dinucleotide phosphate diaphorase*
NCAM	*Neural cell adhesion molecule*
Neu N	*Neuronal nuclear protein*
NID	*Neuronal Intestinal Dysplasia*
NOCD	*Naturally occurring neuronal cell death*
NOM	*Nuclear outer membrane*
NSE	*Neuron-specific enolase*
PBS	*Phosphate buffer solution*
PGP9.5	*Protein gene product 9.5*
PHOX2B	*Paired-like homeobox 2b*
PIPO	*Paediatric intestinal pseudo-obstruction*
PNS	*Peripheral nervous system*
PTEN	*Phosphatase and tensin homolog*
PUMA	*p53 upregulated modulator of apoptosis*
RET	*Rearranged during transfection*
Sox	*Sry-related HMG box*
SPRY2	*Sprouty homolog 2*
TAU	*Tubulin associated unit*
tBid	*Truncated Bid*
VIP	*Vasoactive intestinal polypeptide*

INTRODUCTION

Pediatric motility disorders constitute a complex array of clinicopathologic disturbances ***(Feichter et al., 2010).***

Intestinal pseudo-obstruction is a disorder characterised by the inability of the gastrointestinal tract to propel its contents mimicking mechanical obstruction, in the absence of any lesion occluding the gut ***(Thapar et al., 2018).*** It may affect various components of the bowel neuromuscular apparatus ***(Jain, 2015).*** It is a rare disease with scant epidemiological data ***(Thapar et al., 2018).***

Congenital intestinal neuronal abnormalities have been classified as aganglionosis (Hirschsprung's disease), hyperganglionosis, hypoganglionosis, ganglion cell immaturity, combined forms and certain unclassifiable forms ***(Henna et al., 2011).***

Of all the variations of the enteric nervous system, hyperganglionosis is the most discussed and open to controversy largely because of its association with the diagnosis of intestinal neuronal dysplasia (IND type B) ***(Torre et al., 2002)***.

IND-B can be regarded as a phenotype of relative enteric neural immaturity that may only be recognized with confidence after age of one year and often disappears spontaneously by age of 4 years ***(Kapur and Reyes-Mugica, 2019).*** It is rarely

reported in adult patients ***(Masuda et al., 2017)***. It is characterized by hyperplasia of the myenteric nerves accompanied by giant ganglia ***(Goldblum, 2018).***

IND remains surrounded by controversies related to its definition, etiopathogenesis, diagnostic criteria and therapeutic possibilities ***(Lourencao et al., 2016).***

Immature ganglion cell is known for its relationship with intestinal motility and its impact on postoperative functional outcomes of Hirschsprung's disease ***(Yang et al., 2013).***

The recognition of immature ganglion cells is not always easy. They have a smaller, darker nucleus without a recognizable nucleolus. Special staining methods may be necessary to clarify the ganglion cell morphology and identify immature cells ***(Moore, 2017).***

The BCL-2 gene, an acronym for B-cell lymphoma/leukemia-2 gene, was first identified in B-cell follicular lymphomas ***(Tsujimoto et al., 1985).*** Bcl-2, acts as an important regulator of cell death (***Ujval and Prehn, 2014).***

It can also provide a much more efficacious way in finding the dysplastic (immature) ganglion cells since previous studies showed that it was specifically expressed in them with a positive immunoreactivity in the degenerative and immature ganglion cells but not the mature ganglion cells ***(Wang et al., 2016).***