Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 4 Issue 11 November 2021

Review Article

An Update on the Insight of Embryonic, Etiopathogenesis, Current Surgical Advances Besides the Advocated ERNICA Guidelines for the Management of Rectosigmoid Hirschsprung Disease, and Clinical Referral Score Model for Early Diagnosis with Future Use of Stem Cells - A Systematic Review

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Received: October 01, 2021

Published: October 26, 2021

Abstract

Hirschsprung disease (HSCR), represents a neurocristopathy, secondary to impairment in migration, proliferation, differentiation in addition to survival of the neural crest cells resulting in gut aganglionosis. Its presentation is usually just following birth having an impact on 1/5000 live births all over the world. a significant enhancement in our insight with regards to genetics in addition to correlation with congenital anomalies, possessing a common etiopathogenetic mode of impairment of the generation of neural crest. Besides that various kinds of cell populations like Mast Cells as well as Interstitial cells of Cajal that do not take origin from the neural crest, yet aid In the generation of HSCR have got detailed. Further scientists have Concentrated on the variants of HSCR, that might simulate the Clinical signs but are separate conditions, that possess different treatment strategies in addition to separate prognosis. Thus we decided to conduct a systematic review, where we utilized the search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like embryonic; Early Diagnosis; enteric nervous system; neural crest cells; Vagal; aganglionosis; hypoganglionosis; dysganglionosis; receptor tyrosine kinase RET in ENS migration; Retinoic acid; congenital-hypothyroidism; thymus; Mast Cells; Interstitial cells of Cajal; associated congenital anomalies; pseudo- Hirschsprung disease animal studies; human studies; genetics; stem cells; induced pluripotent stem cells (iPSCs) variant HSCR; from 1985 to 2021 till date. We found a total of 10, 000 articles out of which we selected 67 articles for this updated review. No meta-analysis was done. thus early Diagnosis is essential, with surgical removal of the aganglioic area of the intestine. of Transanal endorectal pull-through (TEPT) is believed to be the better procedure yet several patients experience continuation of symptoms patients. Thus we have tried to discuss the future enhancement of results with the utilization of stem cells, induced pluripotent stem cells (iPSCs) in addition to tissue engineering for aid for the ones that experience recurrence In 30-50% post surgery.

Keywords: Hirschsprung Disease; Neural Crest Cells; Neurocristopathy; Mast Cells; Interstitial Cells of Cajal

Introduction

Hirschsprung disease (HSCR) represents a generational condition implicating the enteric nervous system (ENS)that results secondary to aberrant migration, proliferation, differentiation in addition to survival of the neural crest cells (NCC), resulting in total lack of ganglia in the wall of the gut (a ganglionosis coli). The latin

word for HSCR is megacolon congenitum [1], pointed to a classical escalated ganglia that is present orally towards the implicated area. Neural crest (NC) represents a significant embryonic structure, from which arises an assorted range of cell population inclusive of the ones constituting the ENS. In view of maximum significant etiopathogenesis for the generation of HSCR in this NC aberration, with this belonging into the classification as neurocristopathies [2]. The subsequent total lack of ENS ganglia In the implicated area of the intestine results in functional obstruction, that clinically presents just subsequent to birth. it is a very common generational disorder of the ENS, that takes place in 1/5000 live births (LB) all around world, possessing racial in addition to different regional variations [3]. It occurs more in males [4]. The commonest presenting symptom is an aberrant transition of meconium, that result in more clinical analysis, that finally leads to validation of the diagnosis via imaging, methods as well as biopsy [5]. In maximum subjects, the ultimate treatment strategy is the surgical removal of the aganglionic area of the intestine, nevertheless, up to 30-50% of patients witness recurrent symptoms [6]. On persistence of these symptoms inspite of therapy, the robustness of the gut contents stasis might deteriorate as well as might result in a life threatening Hirschsprung - correlated enterocolitis [7]. The surgical treatment has advanced remarkably in the past decade. This significant escalation in HSCR management has been directly associated with the further advances in paediatric surgical aspects like the generation of a single –stage trans anal pull through (has made sure that minimal scarring following surgery, better pain amelioration, reduction in the hospitalization time, besides being safer as well as possess better efficacy [8]. Despite that, besides suffering from somatic symptoms, they manifest a lot of psychological problems [9]. Having the knowledge that HSCR is a neurocristopathy, the analysis of a patient in whom the diagnosis of HSCR is made needs to be meticulous for looking for the probable presence of other conditions that might be correlated with aberrant NC generation, like medullary thyroid carcinoma, neurofibromatosis, or multiple endocrine neoplasia [10].

Methods

We utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like PCOS;AMH; Rotterdham criteria; Insulin resistance; hypothalamic-pituitary-gonadal (H-P-G) axis influence; animal studies; human studies; transgenerational transfer of PCOS; effects of exaggerated prenatal androgens on offspring; Role of Vitamin D from 1985 to 2021 till date.

Results

We found a total of 10, 000 articles out of which we selected 67 articles for this updated review. No meta-analysis was done

Neurocristopathies

NC represents a structure that is temporary in case of vertebrates, originating from neural folds at the time of generation of a neural tube that possesses cylinder like shape [11]. Inspite of its origin from the neuroectoderm, it does not only generate nervous tissue structures, but following going via epithelial –mesenchymal transition transformation (EMT), its multipotent cells move towards far areas of the generating embryo that gets followed by differentiation into different cell kinds [10]. Mosly NC gets sub classified into 4 main parts i) that vary in their migratory pathways as well as cell kinds, which they finally generate. These are i) cranial/cephalic [12], trunk [13], iii) vagal as well as sacral [14], iv) in addition to cardiac NC [15]. Based on the area, NCC, differentiate into components of the peripheral nervous system (PNS) that is inclusive of the (ENS) but to connective tissue, muscles in addition to bones in the head as well as neck area, besides structures belonging to the eye, ear, melanocytes, chromaffin cells of the adrenal gland, besides a lot more [16]. With the migratory behavior of NC cells akin to the malignancies at the time of metastasis, evaluation of NC generation can yield greater insights in cancer behavior. Hence with the significance of NC apart from the lot of various cell kinds it yields a classic 3 germ-layer model has been posited by the workers of the embryonic generation Boland, an American physician, in addition to pathologist gave the concept of that is a blanket word brought in utilization of a bigger proof conditions that got initiated from the aberrant NC generation. Thus he posited simple neurocristopathies as well as complicated/neurocristopathy syndromes dependent on the complicated nature of variations of neurocristopathies of the primary etiopathogenetic mode apart from the degree of disease. From variations In neurocristopathies the commonest well worked with greater insight are Treachery Collins syndrome, 22q11. 2 deletion syndromes as well as HSCR [17].

Generation if the normal enteric nervous system (ENS)

ENS stands out in the form of a web simulating system depicting the innervation of the gut wall as 2 plexuses present in tunica submucosa as well as ii) tunica muscularis externa. These do not

belong to the parasympathetic/sympathetic enteric nervous system (ENS), this ENS is constituting a 3rd kind of autonomic enteric nervous system (ANS), despite it getting input from both [18]. With its complicated nature with simulation with the central enteric nervous system (CNS) motivated scientists to label it as the brain of the gut''/''second brain''.

Hirschsprung disease etiopathogenesis

With great difficulty in 1948 the breakthrough with treatment came at the time with recto sigmoidectomy Subsequently in addition to repeat surgeries as well as experimental work in 1948 displayed that it was aganglionosis which was the primary cause implicated in the abortal area of the intestine, whereas the enhancement just above the implicated part was just secondary to the stasis caused by this aganglionosis primarily [19]. Subsequent to the molecular biological advancements, the1st genetic cause was reported [36]. Currently utilization of a lot of animal models is done for understanding the pathophysiology of this condition. Stamp., *et al*. [20], evaluated mice possessing a spontaeous null mutations In the endothelin receptor type B (EDNRB). With the mutation the mice couldn't survive the stress of surgery, thus not useful for experimental work. Hence Stamp., *et al*. [20], were forced to do a colostomy for the escalation of life span for studying them in the form of models for HSCR [20]. With the advent of methods like teratogens utilization, surgical methods apart from gene knock out for the induction of HSCR [21]. Now enough evidence exists that HSCR is a heritable disorder, with about 10-20% of subjects revealing a positive family history, whereas In rest it takes place just as a sporadic manifestation [22]. Possessing the knowledge that it is a heterogenous disease, wih complicated inheritance modes in addition to etiology which is multifactorial [23], a lot of genes got responsible for the lack of NCC, populating the gut along with have normal generation into the ENS. Certain of the maximum extensively evaluated, with important genes possessing impairing expression towards the generation of HSCR include RET, GDNF. RET is supposedly a proto-oncogene, that encodes the RET tyrosine kinase receptor. The GDNF gene encodes the GDNF protein (that is from the GDNF family of ligands), that is further a ligand for RET [23]. One more protein possessing significance is GFRα1. The crosstalk amongst these proteins is; generation of a complex by GFRα1 as well as GDNF, that is followed by activation of RET, that then gets autophosphorylated as well as, in turn results In stimulation of the RET pathway, results In controlling of significant embryonic enteric neural crest cells (ENCCs), that is inclusive of migration, proliferation, differentiation [24]. Occurrence of a mutation In these key genes ensure that ENCCs are unable to migrate as well as generate further in a proper way in time. Under normal situations GDNF gets expressed within the mesenchyme in parallel with the generating gut that lures the RET in addition to GFRA expressing ENCCs. The GDNF expression further propagates in a caudal direction, that makes sure that normal colonization by ENCCs occurs In the gut [25]. Besides these significant cross talks, there are a lot of genes in addition to pathways that participate in impaired ENS generation, like EDNRB, PHOX2B, SOX10, apart from a lot of others [26], 25 commonest genes evaluated [27].

Despite the genetics of the pathogenesis of HSCR is well clear, it accounts for about 50% of the total subjects. This Implies that one has to take into account certain other factors. One of them is the retinoic acid signaling [28]. Utilization of mice models for experimental evaluation have illustrated retinoic acid is needed for the normal generation of ENS is retinoic acid. In 2010 Fuetal [29], with utilization of mice that were Rbp4-/- in addition to retinol binding protein deficit that was artificially created, resulting in mild Vitamin A deficit along with double mutations Rbp4-/- in addition to changed RET signaling (Ret+/-) that is a prompting factor for the generation of aganglionosis. Fu., *et al*. [29], observation was that In the situations where just RBP4 deficit was existing only generation of aganglionosis occurred sporadically, if their diet possessed sufficient Vitamin A. Nevertheless, during the existence of concomitant changed RET signaling, the mice generated despite large quatities of Vitamin A In diet. The implication of this is that the impairment of these two pathways simultaneously display synergism [29]. Recently Uribe., *et al*. [30], with the utilization of a zebrafish model, further revealed that retinoic acid is key for ENCCs migration besides survival [30].

Conditions correlated with Hirschsprung disease

The key step following the diagnosis of HSCR is analyzing for the existence of extra aberrations in view of common etiopathogenesis (EP) of HSCR with other conditions correlated that brings the query of their concomitant taking place. Slavikova., *et al*. [31], studied 130 paediatric patients from a cohort, concluding finally that 26. 1% possessed correlation with congenital abnormalities. In case functional situations were correlated with these congenital abnormalities, over 50% of patients possessed correlated diagno-

sis. Immune system impairment occurred a lot of fold of the detailed range of HSCR correlated congenital abnormalities, besides heart aberrations, as well as genitourinary abnormalities [31]. As per Amiel., *et al*. [32], 70% patients presented alone, while 12%of patients possessed chromosomal abnormalities, with over 90% having Down's syndrome. In view of this incidence, Amiel., *et al*. [32], highlighted that the complicated management of a patient where diagnosis of HSCR is done needed meticulous analysis by an experienced clinician known as dysmorphologist [32], like congenital central hypoventilation syndrome, some of which generate Wardenburg syndrome, or Mowat-Wilson syndrome, all of these get classified besides the correlated abnormalities, that takes place simultaneously, whereas HSCR is the primary pathogenetic mode, HSCR has been detailed as a particular part of various syndromes that were classified as neurocristopathies. Evaluation of HSCR with regards to separate syndromes has significantly aided In getting insight of its genetics [33]. The commonest as well as well detailed unique abnormalities in HSCR patients in descending order represent gastrointestinal Tract (GIT), genitourinary, musculoskeletal, cardiovascular, craniofascial in addition to integumentary abnormalities [34]. The spectrum of these simultaneous congenital abnormalities emphasizes the complicated nature, besides the diversity of NCCs, as well as their markedly important part of many apparently unrelated organ systems. Besides the morphological abnormalities, HSCR is further correlated with different functional conditions. Inspite of their importance, occasional articles detail them. Just one article in 1988 by Kusch., *et al*. [35], detailed the correlation among different congenital abnormalities of the large intestine in addition to impairment In generation of the immune system [35]. This seemed unanticipated, knowing that the normal generation of the thymus, the organ that is most significant for the generation of adaptive cellular immunity, based on the crosstalk amongst the generating epithelial thymic primordium, besides the surrounding mesenchyme. This NC obtained mesenchyme takes origin from the akin NC area, from where the future intestinal ganglia originate [36]. The early thymic generation, besides being the stage of organogenesis, possesses significant part of the NC obtained cells. In the latter part of thymic generation, differentiation into perivascular cells as well as probably aid in these significant functions, like the generation of the thymus blood barrier, in addition to the controlling of the endothelial function [37].

A separate understudied HSCR correlated functional abnormality represents congenital hypothyroidism. This also seems astonishing, as it is well proved that the thyroid hormones are key in the appropriate generation of cerebral cortex [38]. Just 5 studies conducted following, the initial detailing of congenital hypothyroidism, In 85, of which 2 are just case reports [31,39]. From the embryonic aspect, this abnormality of generation of thyroid gland can be further thought of as a neurocristopathy, as NCCs participate significantly In the connective tissue constituents generation of the gland as well as its paracalcitonin - generating parafollicular cells [31,40].

Hirschsprung disease as well as Interstitial cells of Cajal

Interstitial cells of Cajal (ICC's) represent pacemaker cells, key for the coordination of normal gastrointestinal motility. Their embryonic initiation is separate from those of the ENS, despite their initial detailing as Interstitial Neurons by Cajal who made their discovery. They get obtained from c-kit positive progenitor cells that originate from mesenchyme cells [41]. Of the different functions of these ICC's, in the context of GIT motility they work as transducers of the neural impulses from the ENS towards the smooth muscles. Further they possess a key part In the development of small waves of electrical action in smooth muscles cells, that is significant for the appropriate rhythmic contractions of peristaltic movements [42]. At the time of gut organogenesis, NCC's possess a direct impact on the differentiation of mesenchymal stem cells into the c-kit precursors of the ICC's, whereas simultaneously, the newly cells that differentiate have an impact on the NCC's in a reciprocal manner by different methods Probably they possess a Controlling part in the NCC's migration through the decrease in GDNF the suggests that a migratory wave of NCCs in an appropriate pathway. Probably they possess a role In stimulation of differentiation into mature components [43]. With regards to HSCR, a high probability exists that ICC's have a equal part In their generation. The morphological studies published, describing the distribution of ICC's in patients with HSCR was In 1990's, besides in early2000. Vanderwinden., *et al.* illustrated a reduction in cellular density besides, impairment of ICC's networks in case of subjects with HSCR [44]. Rolle., *et al*. [45], conducted another morphological study for analysis of the distribution of ICC's. Their observation was that a significant reduction in ICC's obtained via the specimens from HSCR subjects. They further pointed that, the changed ICC's might be implicated in the continuing impairment In the motility following surgery [45]. Conversely, Newman., *et al*. [46], observed no changes In ICC's in HSCR patients, besides not observing that ICC's were implicated

In postoperative motility impairment [46]. A further recent experimental study with the utilization of aganglionic rat model, where at same time scientists did transplantation of neuroepithelial stem cells as well as ICC's into this aganglionic gut. The speeding up of differentiation of the ENS constituents was encountered in contrast to just the transplantation of neuroepithelial stem cells [47].

Hirschsprung disease as well as mast cells

Mast Cells (MCs)s constitute immune cells that conduct their major part in a wide range of separate peripheral tissues where they move from the Bone marrow. The maximum significant part of MCs is their implication in allergic responses, nevertheless, they further aid in normal functions of the body, like wound healing, besides immune tolerance [48]. In context of the GIT, MC's have a controlling part in a lot of key gut functions like epithelial permeability/epithelial barrier integrity, neuro immune response, blood flow along with peristaltic movements [49]. Minimal art concentrated on the part of MCs in the etiopathogenesis of HSCR. Kobayashi., *et al*. [50] in 1999 conducted an experimental study, with utilization of. Immunohistochemistry (IHC)for the evaluation of the quantity of MC's in the ganglionic, transitional as well as aganglionic segment of the large intestine in subjects of HSCR articles. The aganglionic segment possessed a greater quantity in contrast to the rest 2 evaluated segments. The inricate contact of MC's with nerve fibers, their probable part in the growth of nerve fibers in addition to repair, besides in the liberation of nerve growth factor (NGF), pointed that MC's might be implicated for hypertrophy of nerve trunk along with hyperplasia of adrenergic as well as cholinergic nerve fibers that is the classical sign of HSCR [69]. Akin outcomes got replicated by Demirbilek., *et al*. [51]. Further Hermanowicz., *et al*. [52], in addition concentrated on the size of MC's as well as arriving at the conclusion that a significant escalation occurred in both tunica. submucosa in addition to tunica. muscularis externa in case of patients with HSCR [52]. However, the exact part of MC's in case of HSCR EP is not clear [43].

The difficulties in diagnosis correlated with Hirschsprung disease analysis

Following the initiation of 1st signs a patient undergoes anorectal manometry, besides imaging evaluation these days with the utilization of commonest plain abdomino pelvic X Ray in addition to contrast enema. For the validation of definitive diagnosis, classical histopathological examination (HPE) is required, that is believed to be the gold standard, possessing 93-98% sensitivity as well as specificity [53]. Besides aganglionosis, the maximum classical (HPE cues of the disease represent hypertrophy of nerve fibers bundles along with escalation of the histochemical staining for acetyl cholinesterase in addition to irregular nerve fibers In the lamina propria as well as lamina muscularis mucosae [54]. The escalation of acetyl cholinesterase action is believed to be pathognomonic for Hirschsprung disease [55]. A diagnostic confusion might take place if a patients clinical manifestation is akin to hyperplasia HSCR, Nevertheless, the biopsy reveals the existence of ganglia. This class is markedly heterogenous as well as inclusive of intestinal ganglioneuromatosis, isolated hypoganglionosis in addition to existence of immature ganglia, besides others [56]. Hence the common word whose utilization is made for these disorders is ''nonconsensual''. These variants of Hirschsprung disease are mostly known as chronic idiopathic intestinal pseudo obstruction/intestinal hyperperistalsis syndrome/neonatal intestinal pseudo obstruction [57]. The word coined like variants of Hirschsprung disease creates hurdles from 2 ways i) the terminology Hirschsprung disease immediately pointed that aganglionosis exists whereas the main parameter of these disorders is the existence of incomplete lack of ENS ganglia, ii) the etiopathogenesis (EP) of some of these conditions is separate in addition to more intricately correlated with other syndromes. Hence it is further pointed that classification of these entities into a group of Variant ENS [54].

Despite the common existence of diagnosis of HSCR in addition to pseudo HSCR at the time of childhood lot of case reports in literature that detail patients having not been meticulously diagnosed till adulthood. Ito., *et al*. [58] cited a case report of a young 20yr old man, presenting with history of constipation right from childhood at 2 yr, got admitted with cardiac arrest as well as died the next day. On autopsy hypoganglionosis in addition to megacolon –whereas direct etiology of death was robust intestinal necrosis [58]. The ENS, particularly the one present in the colon, grows via age - correlated morphological as well as functional alteration, hence making a diagnosis of gut motility impairment in case of individuals with greater age proves to be tougher [59].

Conclusions in Addition to Future Directions

In contrast to the past (various decades earlier) we have gained much greater insight at present with regards to the embryological angle. Now researchers have unveiled the lot of facets in the etiopathogenesis (EP) in the context of genetics crosstalk. Nevertheless, the biggest challenge at present still persisting is the treat-

ment. A significant enhancement in the surgical treatment, with much greater outcomes for such patients, although a lot of post operative complications get encountered, that result in reduction In the quality of life (QOL) recently. Gabriele Ivana., *et al*. evaluated the functional results of Transanal endorectal pull-through (TEPT) with the utilization of Krickenbeck classification. their observation was that from 2012-21 in their institution., the functional results of HSCR patients following TEPT were elieved to e comparatively good I 50 patients of Hirschsprung disease. Furthermore, the Voluntary bowel movement (VBM), soiling, besides constipation risk of TEPT might get influenced by sex, age at TEPT as well as postoperative complications, respectively, whereas the age at TEPT carried out, might not be correlated with functional results. Further multicenter studies with a larger sample size are necessary to clarify and confirm their observations [60].

Much more advantageous future aspects are concentrated towards stem cells research in addition to tissue engineering. Rollo., *et al.* [61], carried out an experiment, that tried to illustrate three possible situations i) the possibility of human-ENS-obtained cells, that were collected postnatally for the colonization of the embryonic intestine; ii) the ability of postnatally collected aganglionic part of the colonic muscle from a HSCR patient for nurturing the generation of ENS with the utilization of murine obtained embryonic ENS network; iii) the capability of ENS cells collected from the ganglionic part of a HSCR patient's gut to the autologously colonize the aganglionic part of the same patients colonic muscle. All the 3 situations proved to be viable. The maximum significant conclusions derived was that autologous transplantation is feasible in view of fulfilling the most significant criteria; the probability of garnering of ENS obtained cells from a HSCR patient, the ability of aganglionic muscle for getting. besides supporting of ENS de novo getting established, as well as lastly, but significantly the capacity as well as how competent the postnatal ENS obtained cells for the colonization of the colonic muscle of the same patient. These outcomes appear attractive, yet markedly distant from routinely utilization of these In the clinical scenario. The major hurdle is development of enough amounts of the progenitor cells in addition to look for adequate ways for efficaciously transplant them to a markedly greater area of the of the aganglionic gut [61]. Shlieve., *et al*. [62]. In 2017 evaluated the probability of ENCC's obtained from human organoids. These outcomes have demonstrated that tissue engineering as well as towards stem cells research might prove to be promising in future for the treatment of gut neuropathies [62]. The utilization of an akin technology was conducted in the same year by Workman., *et al.* utilizing embryonic, besides induced pluripotent stem cells (iPSCs) for generation of the human gut [63]. These days cell therapies with the utilization of iPSCs holds promise with regards to regenerative treatment, thus supposedly the insight gained by them in other diseases might get broadly used [64]. Genetic manipulation is a separate strategy for modern therapy. A state of the art CRISPR/CAS 9 technique has got evaluated as a method for repairing the RET mutations in ENCCs, implicated in their impaired migration as well as differentiation [65]. All these Innovative strategies are thought to offer great promise that might be alternatives to complementary to the surgical patients, yet still lot of experimental work is needed in this field prior to optimizing their results. ERNICA, (the European Reference Network for rare inherited and congenital digestive disorders) gave recommendations in crucial topics covering the care pathway for rectosigmoid HSCR were generated by an international workgroup of experts from 8 European countries preset in ERNICA European Reference Network from the disciplines of surgery, medicine, histopathology, microbiology, genetics, as well as patient organization representatives. Advocated statements were dependent on comprehensive review of the accessible literature in addition to expert consensus. utilization of AGREE II along with GRADE strategies were utilized at the time of its generation. The levels of proof in addition to levels of acceptability were recorded [66]. they generated thirty-three statements with regards to 9 crucial aspects of Hirschsprung disease. Most of the advocated statements were dependent on expert opinion. thus concluding that in occasional or low-prevalence diseases like Hirschsprung disease (HSCR), there are restricted high-quality clinical proof that exist. Consensus- dependent guidelines for care were reported [66].

Lately In 2021 Khorana., *et al*. [67], generated a Clinical Referral Score Model for Early Diagnosis of HSCR. Five clinical parameters correlated with the diagnosis of HSCR were the following: i) age under one month, ii) male gender, iii) term infants iv) history of delayed passage of meconium 48 h following birth, in addition tov) possessed history of enterocolitis. Patients with suspected HSCR, who had a clinical score of 4-7, had a greater likelihood to be HSCR, besides getting suggested for early referrals for more investigations, that were contrast enema, along with rectal suction biopsy. In case of a low probability of HSCR, clinical observation and fol-

low-up are still required until the symptoms have been resolved. This clinical scoring system can be used as a screening tool to avoid delay in diagnosis and complications of HSCR, thus avoiding late presentation In adulthood with catastrophic outcome [67].

Bibliography

1. FIPAT. "Terminologia Embryologia". 2ND ed. Federative International Programme for Anatomical Terminology (2017): 329.
2. Torroglosa A., *et al*. "Epigenetics in ENS development and Hirschsprung disease". *Developmental Biology* 417 (2016): 209-216.
3. Bradnock TJ., *et al*. "Hirschsprung disease in the UK and Ireland: incidence and Anomalies". *Archives of Disease in Childhood* 102 (2017): 722-727.
4. Henderson D., *et al*. "Hirschsprung disease in twins :A systematic review and, meta-analysis". *Pediatric Surgery International* 33 (2017): 855-859.
5. Groerer S. "Paediatr. intestinal motility disorders". *World Journal of Gastroeterology* 21 (2015): 9683-9687.
6. ThakkarHS., *et al*. "Functional outcomes in Hirschsprung disease:a single institutions 12 year experience". *Journal of Pediatric Surgery* 52 (2017): 277-280.
7. Roorda D., *et al*. "Redosurgry with longitudinal resection for dilated bowel in Hirschsprung disease. :an illustrtiv case series". *International Journal of Colorectal Disease* 34 (2019): 1983-1987.
8. Ahmad Wani S., *et al*. "Short term and long termoutcome of single stage trans anal pull through for Hirschsprung disease In neonates and infants". *Journal of Neonatology* 9 (2020): 277.
9. Rintala RJ and Pakarinen MP. "Long termoutcomes of Hirschsprung disease". *Seminars in Pediatric Surgery* 21 (2012): 336-343.
10. Sato TS., *et al*. "Neurocristopathies: Enigmatic appearances of neural crest cells derived abnormalities". *Radiographics* 39 (2019): 2085-2102.
11. LeDouarin NM and Dupin E. "The neural crest In vertebrate evolution". *Current Opinion in Genetics and Development* 22 (2012): 381-389.
12. Cordero DR., *et al*. "Cranial neural crest cells on the move:their roles In craniofascial development". *American Journal of Medical Genetics Part A* 155 (2011): 270-279.
13. Vega Lopez GA., *et al*. "Vagal neural crest cells: formation, migration and beyond". *The International Journal of Developmental Biology* 61 (2017): 5-15.
14. Wang X., *et al*. "Analysis of the sacral neural crest cells contribution to the hindgut enteric nervous system in the mouse embryo". *Gastroeterology* 141 (2011): 992-1002. e6.
15. Chan WY., *et al*. "Cardiac neural crest cells of the mouse embryo. :axial level of origin, migratory pathway and cell Anatomy of the splotch (SP2H)mutant effect". *Development* 131 (2004): 3367-3379.
16. Bronner Fraser M and LeDouarin NM. "Development and evolution of the neural crest: an overview". *Developmental Biology* 366 (2012): 2-9.
17. Zhang N., *et al*. "The neural crest: Aversatile organsystem". *Birth Defects Research Part C - Embryo Today: Reviews* 102 (2014): 275-298.
18. Rao M and Gershon MD. "Enteric nervous system Development :What could possibly go wrong?" *Nature Reviews Neuroscience* 19 (2018): 552-565.
19. Goldstein AM and Copx NJ. "Complex simplicity and Hirschsprung disease". *The New England Journal of Medicine* 380 (2019): 1478-1479.
20. Stamp LA., *et al*. "Surgical intervention to rescue Hirschsprung disease in a rat model". *Journal of Neurogastroenterology* 21 (2015): 552-559.
21. Fujiwara N., *et al*. "Animal models of Hirschsprung disease:state of the art in translating experimental research on the bedside". *European Journal of Pediatric Surgery* 29 (2019): 361-367.
22. Belknap WM. "The pathogenesis of Hirschsprung disease". *Current Opinion in Gastroenterology* 18 (2002): 74-81.
23. Tjaden NEB and Trainor PA. "The Developmental etiology and pathogenesis of Hirschsprung disease". *Translational Research* 162 (2013): 1-15.

24. Tansey MG., *et al*. "GFR apha-mediated localization of RET to lipid rafts for effective downstream signaling differentiation and neuronal survival". *Neuron* 25 (2000): 611-623.

25. Natarajan D., *et al*. "Requirement of signaling by receptor tyrosine kinase RET for directed migration of enteric nervous system progenitor cells during mammalian embryogenesis". *Development* 129 (2002): 5151-5160.

26. Elworthy S., *et al*. "Phox2b function in the enteric nervous system is conserved in zebrafish and is sox10 dependent". *Mechanisms of Development* 122 (2005): 659-669.

27. Klein M and Varga I. "Hirschsprung disease-Recent understanding of embryonic aspects, etiopathogenesis and future treatment avenues". *Medicinas* 56 (2020): 611.

28. Simkin je., *et al*. "Retinoic acid upregulates Ret and induces chain migration and population expan sion In Vagal neural crest cells tocolonize the embryonic gut". *PLoS ONE* 8 (2013): e64077.

29. Fu Metal. "Vitamin A facilitates enteric nervous system precursor migration by reducing Pten accumulation". *Development* 137 (2010): 631-640.

30. Uribe RA., *et al*. "Retinoic acidtemporarily orchestrates colonization of the gut by Vagal neural crest cells". *Developmental Biology* 433 (2018): 17-32.

31. Slavikova T., *et al*. "An embryological point of view on associated congenital anomalies of children with Hirschsprung disease". *Bratislava Medical Journal* 116 (2015): 640-647.

32. Amiel J., *et al*. "Hirschsprung disease, associated syndromes and genetics: a review". *Journal of Medical Genetics* 45 (2007): 1-14.

33. Moore SW. "Chromosomal and related Mendelian syndromes associated with Hirschsprung disease". *Pediatric Surgery International* 28 (2012): 1045-58.

34. Moore SW. "The contribution of associated congenital anomalies in understanding Hirschsprung disease". *Pediatric Surgery International* 22 (2006): 305-315.

35. Kusch NL., *et al*. "Clinicoimmunologic comparisons of developmental defects of the large intestine in children". *Klinicheskaia khirurgiia* (1988): 10-12.

36. Itoi M., *et al*. "Mesenchymal cells are required for functional development of thymic epithelial cells". *International Immunology* 19 (2007): 953-964.

37. Foster K., *et al*. "Contribution of neural crest derivedcells In the embryonic and adult thymus". *Journal of Immunology* 180 (2009): 3183-3189.

38. Auso E., *et al*. "Moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration". *Endocrinology* 145 (2004): 4037-4047.

39. Monroy-Santoyo S., *et al*. "Higher incidence of thyroid agenesis in Mexican newborns with congenital hypothyroidism associated with birth defects". *Early Human Development* 88 (2012): 61-64.

40. Varga I., *et al*. "The phylogenesis and ontogenesis of the human pharyngealregion focused on the thymus, parathyroid and thyroidglands". *Neuroendocrinology Letters* 29 (2008): 837-845.

41. Groerer S and Rolle U. "Interstitial cells of Cajal in the normal human Gut and in Hirschsprung disease". *Pediatric Surgery International* 29 (2013): 889-897.

42. Al-Shabol OA. "The importance of Interstitial cells of Cajal in the Gastrointestinal Tract". *Saudi Journal of Gastroenterology* 19 (2013): 3-15.

43. Radenkovic G., *et al*. "Development of Interstitial cells of Cajal in the human digestive tract as the result of induction of Mesenchymal and neural crest cells". *Journal of Cellular and Molecular Medicine* 22 (2007): 778-795.

44. Vanderwinden JM., *et al*. "Interstitial cells of Cajal and in Hirschsprung disease". *Gastroeterology* 111 (1996): 992-901-10.

45. Rolle U., *et al*. "Altered distribution of Interstitial cells of Cajal in Hirschsprung disease". *Archives of Pathology and Laboratory Medicine* 126 (2002): 928-933.

46. Newman CJ., *et al*. "Interstitial cells of Cajalare normally distributed in both ganglionated and aganglionic bowel in Hirschsprung disease". *Pediatric Surgery International* 19 (2003): 662-668.

47. Zhang L., *et al*. "Cotransplantation of neuroepithelial stem cells with Interstitial cells of Cajal improves neuronal differentiation in a rat aganglionic model". *Journal of Pediatric Surgery* 51 (2017): 1188-1195.

48. Ravanbakhsh N., *et al*. "The role of Mast Cells In Paediatr Gastrointestinal disease". *Annals of Gastroeterology* 32 (2019): 338-345.

49. Bischoff SC., *et al*. "Human Mast Cells, bacteria and intestinal motility". *Immunology Review* 217 (2007): 329-337.

50. Kobayashi H., *et al*. "Mast Cells and gut nerve development: implications for Hirschsprung disease and intestinal neuronal dysplasia". *Journal of Pediatric Surgery* 34 (1999): 543-548.

51. Demirbilek S., *et al*. "Mast Cells distribution and colonic mucin composition in Hirschsprung disease and intestinal neuronal dysplasia". *Pediatric Surgery International* 17 (2001): 136-139.

52. Hermanowicz A., *et al*. "Topography and morphometry of intestinal Mast Cells in children with Hirschsprung disease". *Folia Histochemica et Cytobiologica* 46 (2008): 65-68.

53. Das K and Mohanty S. "Hirschsprung disease-Current diagnosis and management". *Indian Journal of Pediatrics* 84 (2017): 618-623.

54. Moore SW. "Advances in understanding functional variations in the Hirschsprung disease spectrum (variant Hirschsprung disease)". *Pediatric Surgery International* 33 (2016): 285-298.

55. Szylberg L., *et al*. "Diagnosis of Hirschsprung disease with particular emphasis on histopathology:a systematic review of current literature". *Przegląd Gastroenterologiczny* 9 (2014): 264-269.

56. Friedmacher F., *et al*. "Classification and diagnostic criteria of variants of Hirschsprung disease". *Pediatric Surgery International* 29 (2013): 885-872.

57. Puri P. "Intestinal dysgangliosis and other duisorders of intestinal motility". In Paediatr Surgery, 7th ed; Coran AG, Ed; Mosby: Philadelphia, PA, USA 102 (2012): 1279-1287.

58. Ito T., *et al*. "Megacolon in an adult case of hypogangliosis, a pseudo- Hirschsprung disease:a autopsy study". *Internal Medicine* 47 (2008): 421-425.

59. Hanani M., *et al*. "Age related changes In the morphology of themyenteric plexus of the human colon". *Auton Neuroscience* 113 (2004): 71-78.

60. Gariele Ivana G., *et al*. "Functional outcomes of patients with short-segment Hirschsprung disease after transanal endorectal pull-through". *BMC Gastroenterology* 21 (2021): 85.

61. Rolle BN., *et al*. "Enteric neural cells from Hirschsprung disease patients form ganglia in autologous an neuron al colon". *Cellular and Molecular Gastroenterology and Hepatology* 2 (2016): 92-109.

62. SchlieveCR., *et al*. "Neural crest cells Implantation restores enteric nervous system function and alters the Gastrointestinal Transcriptome in human tissue engineered small intestine". *Stem Cell Report* 9 (2017): 883-896.

63. Workman MJ., *et al*. "Engineered human pluripotent stem cells-derived intestinal tissues with a functional enteric nervous system". *Nature Medicine* 23 (2017): 49-59.

64. Csbonyeova M., *et al*. "Induced pluripotent stem cells and their implication for re generative medicine". *Cell Tissue Bank* 16 (2014): 171-180.

65. Jaroy EG., *et al*. "'Too much guts and not enoughbrains'': (epi) Genetic mechanisms and future therapies of Hirschsprung disease". *Clinical Epigenetics* 11 (2019): 1-11.

66. Kyrklund K., *et al*. "ERNICA guidelines for the management of rectosigmoid Hirschsprung's disease". *Orphanet Journal of Rare Diseases* 15 (2020): 164.

67. KhoranaJ., *et al*. "Development of Clinical Referral Score Model for Early Diagnosis of Hirschsprung's Disease in Suspected Pediatric Patients". *Healthcare* 9 (2021): 678.

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