THE WALKING THRU THE PAST AND THE PRESENT OF HIRSCHSPRUNG DISEASE

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(abstract): Hirschsprung’s disease or congenital megacolon is one of the differential diagnoses of chronic constipation mostly in infancy and may indeed represent a challenge for pediatricians, pediatric surgeons, and pediatric pathologists. The diagnosis relies clearly on the identification of the absence of ganglion cells at the plexuses (submucous and myentericus) of the bowel wall. Hirschsprung’s disease is usually located at the terminal (distal) rectum with potential pre-terminal or proximal extension to the less distal large bowel (sigmoid colon). Astonishingly, there is some evidence that Hindu surgeons of prehistoric India may have been exposed and had considerable knowledge about Hirschsprung’s disease, but this disease is notoriously and eponymously named to Dr. Harald Hirschsprung (1830-1916), who brilliantly presented two infants with fatal constipation at the Berlin conference of the German Society of Pediatrics more than one century ago. Hirschsprung’s disease has been originally called “Die Hirschsprungsche Krankheit”). More than 100 years following his meticulous and broad description, Hirschsprung’s disease is still a puzzling disease for both diagnosis and treatment. Hirschsprung’s disease remains a critical area of clinical pediatrics and pediatric surgery and an intense area of investigation for both molecular and developmental biologists. Keywords: DR. HARALD HIRSCHSPRUNG, HIRSCHSPRUNG’S DISEASE, CONGENITAL MEGACOLON, HISTORY.

Medical history is fascinating and, since its beginning, it was meant to enlighten scientific issues, booster the medical profession, and celebrate the traditions or tales of particular places. Harald Hirschsprung, who presented two infants with fatal constipation at the Berlin conference of the German Society of Pediatrics more than one century ago. Is known in medicine for his eponym of intestinal aganglionosis. Events running before and after Dr. Hirschsprung’s discovery may drive interest in medical students and doctors to review the diagnostic procedures of this intriguing disease and recognize the enormous input given from microscopy and pathology to this diagnosis.

Hirschsprung disease, first described in detail by Harald Hirschsprung in 1886, is a congenital disorder characterized by the absence of ganglion cells in the myenteric and submucosal plexuses of the gastrointestinal tract, leading to functional bowel
obstruction. Despite its long history, the scientific community is still unraveling the complexities and intricacies that define this disease. As a condition that impacts thousands of newborns globally each year, Hirschsprung disease poses unique clinical challenges that necessitate a multidisciplinary approach involving pediatricians, gastroenterologists, surgeons, and geneticists, among others.

This article aims to walk through the historical landmarks that have shaped our understanding and management of Hirschsprung disease, from its initial identification to the modern era of molecular genetics and targeted therapies. It will explore the diagnostic and therapeutic advancements that have transformed patient outcomes and shed light on the current research frontiers that hold the promise of even better management strategies. Additionally, the article will scrutinize the existing gaps in our knowledge and identify areas where further research is crucial for more effective treatment and improved quality of life for affected individuals.

By bridging the past and present, this comprehensive review provides not only a historical perspective but also an up-to-date overview of Hirschsprung disease, thereby serving as a valuable resource for clinicians, researchers, and medical students alike.

**MATERIALS AND METHODS**

A comprehensive search strategy was devised to include articles from the earliest available records to September 2023. Keywords and phrases used in the search included but were not limited to: “Hirschsprung Disease”, “Congenital Aganglionic Megacolon”, “Colonic Aganglionosis”, “Ganglion Cells”, “Treatment”, “Diagnosis”, “Genetics”, and “Pathophysiology”.

The databases utilized for the literature search in this review include PubMed, Web of Science, and ScienceDirect. These databases were chosen for their wide scope, accessibility, and credibility within the scientific community.

The studies were selected based on the following inclusion criteria: Original research articles, reviews, case studies, and clinical trials focused on Hirschsprung disease / Articles published in peer-reviewed journals / Studies that contributed to the historical understanding or current advancements in diagnosis, treatment, and management of the disease.

The exclusion criteria included were: Articles not available in English / Duplicate studies or those that did not contribute new information / Papers lacking methodological rigor, as assessed by the authors.

The data was then organized into themes pertaining to the historical milestones, diagnostic methods, treatment options, and future research avenues in Hirschsprung disease. This thematic organization facilitated the narrative synthesis of existing literature and helped identify gaps for future research.

By adhering to this methodological framework, this review aims to present a balanced and comprehensive overview of Hirschsprung disease, tracing its historical roots and elucidating its present landscape to identify the most promising paths for future research and clinical practice.

**BRIEF HISTORY**

Young Harald Hirschsprung was born in 1830. He decided not to join the family’s tobacco company to study medicine. Medical studies would become an indirect reason for Hirschsprung’s name to gain immortality. For more than 100 years congen-
The walking thru the past and the present of Hirschsprung disease

ital intestinal aganglionosis, whose macroscopic pathology he described in such detail, has been known worldwide as Hirschsprung’s disease (1).

Harald Hirschsprung (1830-1916) was the founder of Danish pediatrics, and during his work as professor and chief physician of the Queen Louise Children’s Hospital, he made the hospital a home of Danish pediatric research. Dr. Hirschsprung positioned Danish pediatrics internationally, had close relationships with foreign scientific societies and used to attend pediatrics congresses in Germany and Austria every year (fig. 1).

Fig. 1. Harald Hirschsprung
(Source: https://ugeskriftet.dk/videnskab/harald-hirschsprung-og-den-kongenitte-aganglionose)

In 1886, Hirschsprung held the lecture “Stuhlträgheit Neugeborener in Folge von Dilatation und Hypertrophie des Colons” in Berlin at the annual congress of the German Society for Children’s Diseases. He was referring to two cases of the disease that Hirschsprung had observed in 1880 and 1885 respectively at the Dronning Louises children’s hospital. In the introduction to the lecture, he said: “I take the liberty to present to this erudite assembly two presentations of an unusual nature and at the same time briefly explain the associated medical histories (1).” The first presentation was described as follows: “As you can see, it is a large intestine, but of such a size that it will no doubt surprise you to learn that the intestine came from a child who died only at 11 months of age.” In the presentation it was also said that the colon, in addition to being dilated, was also significantly thickened. The dilatation extended into the rectum which appeared normal. The child, who had been constipated since birth, had worsened at eight months of age when Hirschsprung first saw it. Constipation required frequent enemas, the abdomen became strongly prominent, and the child lost weight rapidly. Eleven months later it died. The second case described by Hirschsprung was similar (2).

In the following years Hirschsprung saw several similar cases of the disease and wrote about this condition in one of his works: “It is strange that a form of disease like this which nevertheless produces such prominent symptoms and is of such great importance for the patient is left completely unmentioned in the pediatric literature. However, given my experience, I cannot believe that the condition must really be that rare. But maybe it will happen so often that attention needs to be paid just to make the cases more frequent”. This assumption turned out to be correct. In the following years, an increasing number of reports of these cases of the disease, which were already internationally referred to as Hirschsprung’s disease, were mentioned.

Hirschsprung was convinced that the
disease was congenital, however, it was not until the late 1940s that basic aganglionosis in the rectosigmoid was detected and thus the basis for rational surgical treatment was simultaneously created (3).

Doctor Harald Hirschsprung

Dr. Hirschsprung, who graduated with a degree in medicine in 1855, showed since his first steps into medical career a strong interest in pediatrics, becoming astoundingly the chief physician of the only children’s hospital in Copenhagen just fifteen years later. The appointment as professor of pediatrics came in 1877 and Dr. Hirschsprung became director of a larger children’s hospital in Copenhagen from 1979 until 1904, when he retired. The new children’s hospital was magnificently named after Denmark’s Queen Louise (The Queen Louise Hospital for Children). Dr. Hirschsprung was fond of anatomical variations, peculiar aspects of medicine, and intriguing diseases. He was a brilliant teacher with loyal and faithful students. Between 1880 and 1885, Hirschsprung came across two infants with similar clinical presentation. The first child had bowel problems that persisted soon after birth with absence of spontaneous bowel movements. Daily enemas and laxatives were necessary. The second case had similar bowel distensions with terminal bouts of diarrhea variably alternating with impossibility to evacuate. Notwithstanding the scarcity of information continuous therapy was applied, but, unfortunately, both children eventually died and a postmortem examination was performed. At the autopsy, the rectum was narrowed, but there were striking dilation of the bowel loops with some ulceration of the mucosa associated with thickening of the bowel wall. In his publication, Dr. Hirschsprung summarized his findings and drew attention to the typical clinical presentation of both cases. In an opinion, which is worldwide shared, his meticulous and comprehensive description is not the first one to indicate details of this disease, but he provided a complete and excellent account of this entity in consideration of his clinical experience and practice in pediatrics. The name “Hirschsprung’s disease” came into widespread use shortly before the end of the 20th century and, in 1916, Hirschsprung himself added an additional 10 more cases before his death (2).

Pre-Hirschsprung Era

The examination of the scientific literature seems indicate that approximately 20 similar cases have been recorded between 1825 and 1888. However, there is evidence that Hindu surgeons of prehistoric India had considerable knowledge about Hirschsprung’s disease. Sushruta’s description of a disease called Baddha Gudodaram is extraordinarily analogous to that of Hirschsprung’s disease. Semantically, it seems indicate “abdominal distension due to blocked rectum”.

According to Sushruta, Baddha Gudodaram is a type of disease caused by (functional) blockage of the ano-rectal canal. The affected child or, even, young adult may show rectum and distal colon stuffed with gas, “stones” (fecaliths), “hair” (undigested fibers), and, obviously, feces. In the child, there is an abdominal distension, which is characteristically seen between the heart and the umbilicus. Scanty stools are evacuated with greatest difficulty, and, eventually, it was reported that the patient might vomit feculent fluid. However, the pre-Hirschsprung era is not complete, if additional reports are not also mentioned.
The Sushruta Samhita is an ancient volume of Ayurvedic surgery compiled by Sushruta (circa 1200-600 BC). Passages of interest were identified by browsing through the authentic English translation of the old compendium. The accuracy of the translation was verified by comparing it with the original Sanskrit verses with the help of a Sanskrit scholar. A condition called Baddha Gudodaram, described in the Samhita, closely resembles Hirschsprung’s disease. There are indications that the ancient Indians even deciphered the etiology as defective vayu alias vata (2).

Although the disease was considered incurable, a palliative operation was discussed. Descriptive details of the operation match those of sigmoid colostomy. Evidence from the Sushruta Samhita indicates that Hindu surgeons in prehistoric India probably had considerable knowledge of Hirschsprung’s disease. Further research corroborating other sources of evidence is needed to confirm this claim (4).

Indeed, Fredericus Ruysch, a Dutch anatomist in Amsterdam (Netherland) in 1691 described a 5-year-old girl with abdominal pain. It seems that the usual treatment to relieve pain was permanently inefficacious and the child continued to pass flatulence. No evacuation was practically possible and the child ultimately died (fig. 2).

Domenico Battini, an Italian physician of the 19th century described a child that he followed up for 10 years with severe constipation. The child died and the autopsy demonstrated severe dilatation of the colon. The published Italian contribution showed...
not only a very careful clinical evolution of
the child, but also provided a detailed aut-
opsy with examination of the abdominal
viscera. Particular mention to the morpho-
logical alterations occurred in the large
bowel were present in the original Italian
publication. Through the examination of
the reports, Fiori concludes that Dr. Battini,
nearly one century before Hirschsprung,
may have originally achieved its target in
reporting an archetypal case of megacolon
of congenital type. Distinctively, a num-
ber of characteristic features, including fami-
liarity and the peculiar selective involvement
of “neural layers” of the bowel, that later
became characteristic of Hirschsprung’s
disease, were remarkably well postulated
by Dr. Domenico Battini. To increase the
controversy between Denmark and Italy as
well as other countries, there may be a few
more reports that need to be listed (5).

In 1836, Ebers reported a 17-year-old
boy with a history of constipation since
birth or, perhaps, as toddler, while Jacobi
had also described two neonates with intes-
tinal obstruction in 1869. Fragmentary
reports of children who died of severe con-
stipation appeared also in the literature in
the pre-Hirschsprung era. In fact, Gee re-
ported the autopsy findings of a 4-year-old
child with a “spasm” of the sigmoid colon
without involving of the rectum in 1884,
while Bristowe described the outcome of
an 8-year-old girl who died of mechanic
ileus after longstanding severe constipation
of the bowel (6).

Dr. Hirschsprung died on April 11,
1916, but his supreme legacy to clinical pediatrics, pediatric surgery, and pediatric pathology is unmatched with contributions that go further than severe constipation in children or the disease harboring his name (“Hirschsprungshe Krankheit”) (fig. 3).

Fig. 3. A typical case handled by
Hirschsprung in his hospital
(Source: https://revista.svhm.org.ve/
ediciones/2008/1-2/art-3/)

The Danish pediatrician observed and
described in detail several diseases, includ-
ing pyloric stenosis and intussusception. Dr. Hirschsprung indicated guidelines for management of a broad spectrum of pediat-
ric diseases, including contributions in the
area of teratology and clinical dysmorphol-
ogy. These contributions are now part of
the didactic activity and scientific investi-
gation of innumerable professors and re-
searchers of Pediatrics, Pediatric Surgery,
and Pediatric Pathology. He participated
actively to the building of the children’s
hospital and his dedication to children con-
stant. Queen Louise wanted the wall spaces
above doors to harbor biblical quotations
for the edification of the sick children, but
Dr. Hirschsprung considered more appro-
appropriate to give the children an environment that could bring some quietness. In consideration of the sensibility of the children, he firmly refused the holy quotations and suggested colorful and beautiful wall decorations of animals and flowers, which in the end were well accepted by the Danish crown to be inserted in the wall spaces above doors (7).

The Post-Hirschsprung Era

Recently, the interest has focused on the diagnosis of Hirschsprung’s disease mainly because of the jeopardy of methods used to make the diagnosis and their accuracy. Being a genetic disease quite diverse, main topics on Hirschsprung’s disease involve, indeed, the investigation of the best diagnostic marker for Hirschsprung’s disease and changes that may take place during ganglion cell maturation. Hirschsprung’s disease is now known as the most common cause of neonatal lower intestinal obstruction occurring in 1:5000 live birth newborns. Hirschsprung’s disease involves in about three quarters of cases male children, and its incidence is variable according to ethnics (8). The caudal migration of the primordial neural crest cells starts at the upper end of the gut following progressive-ly the vagal fibers distally. A delay or arrest in this migration induces failure of the neural crest cells to reach the distal bowel with consequent congenital abnormal nerve innervation of the bowel. There is a caudo-cranial severity, which means from the internal anal sphincter extending proximal-ly for a variable length of gut. Pathophysiological, there is a proximal intestine, which is dilated and progresses to an abrupt or, alternatively, gradual transition to a normal calibrated distal bowel. This distal intestinal segment shows typically a funnel like or cone shaped zone in between (the so-called “transition zone”). Moreover, there is a proximal muscle hypertrophy. This anatomic and prominent feature of the colon, located proximal to the aganglionic segment, represents undoubtedly an effort to overcome the partial obstruction. The bowel becomes distended with thickening of its wall, and the degree of dilatation and hypertrophy depends intricately upon both the time and degree of obstruction and obviously, indirectly, to the age of the patient. Clinical presentation settings include failure to pass meconium within the 24-hrs. of life considering that 98% of newborns pass meconium in less than 24-hrs. of age, neonatal intestinal obstruction syndrome (abdominal distension, refusal to feed, and vomiting of bilious type), and recurrent enterocolitis (mainly infants less than 3 months of life), toxic megacolon, spontaneous perforation, and chronic constipation with persistent failure to thrive. Toxic megacolon includes fever, abdominal distension, bile-stained vomiting, explosive diarrhea, dehydration, and shock. History includes failure to pass meconium, painless abdominal distension, and, obviously, constipation. Physical examinations of children with Hirschsprung’s disease includes enlarged abdominal circumference with numerous fecal masses (9). Digital or post-evacuation examinations reveal hypertonic anal sphincter, typical empty rectum, and hard fecal mass. Radiology (plain abdominal X-ray both erect and supine as well as contrast enema) typically shows narrow distal segment, funnel-shaped dilatation characteristically localized at level of transition zone as well as marked dilatation of the proximal colon. Moreover, a poor emptying of barium throughout the colon in 24 hours delayed films is also found. A differential diagnosis of “psychogenic” stool is requested and, in this latter case,
the barium generally collects in the distal recto-sigmoid colon. Electro manometry shows absence of the recto-anal inhibitory reflex (RAIR) when the rectum is distended. RAIR is defined as the reflex of relaxation of the internal anal sphincter following rectal distension (balloon). RAIR (+) means normal, while lack of RAIR, RAIR (-), means Hirschsprung’s disease. Bedside or outpatient procedures seem to give no complications (10). The test is unreliable if the gestational age plus post-natal age is less than 39 weeks and birth weight is less than 2.7 kg. However, if, at neonatal age, electro manometry is useless, it represents a good screening tool in infancy and childhood. Ultrasonography is important to rule out associated anomalies and a genetic counselling may be considered appropriate according to the familiarity and the phenotype of the patients affected with Hirschsprung’s disease. Rectal biopsy is the definitive diagnostic test showing absence of ganglion cells, presence of nerve hypertrophy, and increased acetyl-cholinesterase activity. It may include either a suction mucosal biopsy (at different levels) or a full thickness biopsy. Suction, transmural, and jumbo biopsies are the usual biopsies taken in an infant with severe constipation. It is a general opinion that pediatricians play a major role in diagnosing Hirschsprung’s disease and dysmorphic features remain important landmarks that need to be identified first by clinical pediatricians and, later discussed with clinical geneticists. Typically, Hirschsprung’s disease is clinically identified as a solitary gastrointestinal anomaly in a full term, otherwise healthy newborn or infant, but associated anomalies do occur in about 1/5 of cases, including uro-genital system (11%), cardiovascular system (6%), gastro-intestinal system (6%), and other systemic congenital defects (8%). In as many as 1/10 of children with Hirschsprung’s disease, the condition of prematurity has been reported. Trisomy 21 syndrome (Down syndrome) occurs in approximately 1/20 of children with Hirschsprung’s disease. The work of the pathologists is impressive and their criteria for diagnosing Hirschsprung’s disease are quite straightforward and easy to follow in classic cases. It is important to highlight that not all-severe constipation mean automatically Hirschsprung’s disease. Both the lack of ganglion cells and the hypertrophy of nerve fibers are pathologic landmarks of Hirschsprung’s disease (8).

The diagnosis and surgical treatments of Hirschsprung’s disease have undergone various changes in the last few decades because of establishment of laparoscopic procedures. A nationwide retrospective study conducted in Japan he used the patient data were collected in 4 phases: Group 1, between 1978 and 1982; Group 2, between 1988 and 1992; Group 3, between 1998 and 2002; and Group 4, between 2008 and 2012. The results of the study were that primary operations without laparotomy, including TAEPT and laparoscopy-assisted operations, have become the first choice for the definitive surgical treatment of HD in Japan. The mortality rate has decreased over time. However, the mortality rate of small intestinal aganglionitis is still relatively high. The development of new treatment strategy for small intestinal aganglionitis is called for (11).

In the year 2022 a new surgical procedure successfully addresses a common lingering challenge - incontinence - faced by some families with young children who have undergone surgery for Hirschsprung disease. This first-of-its kind procedure was pioneered by surgeons in the Division of Colorectal and Pelvic Reconstruction at
Children’s National Hospital, led by Division Chief Marc Levitt, M.D. The new pilot study shows long-term outcomes for seven patients between the ages of 2 and 18 who underwent the novel technical approach called sphincter reconstruction. Each of the seven were diagnosed with an anatomic or physical issue contributing to their incontinence. It was during a repair procedure for the first patient that Dr. Levitt and his team had the idea of a technique for sphincter reconstruction. After that, six more patients with similar anatomy were offered the procedure.

The study regarding transcriptional Profiling, Functional Analysis, and Organoid Modeling of Intestinal Mucosa in Hirschsprung Disease it had as a conclusion that despite normal ganglionic structure, the section of colon adjacent to the aganglionic region in Hirschsprung disease and patients has perturbed gene expression which resembles the aganglionic segment. Transcriptional and functional changes in colonic epithelium are persevered in the ganglionic colon used for pull-through surgery. This may explain persistence of enterocolitis despite surgical excision of aganglionic colon and subsequent endorectal pull-through performed with aganglionic colon during correction of Hirschsprung disease (12).

Current evidence suggests that transplantation of enteric nervous system stem cells, sourced from easily accessible postnatal gut, could be a viable alternative treatment for Hirschsprung disease and ultimately for a number of other congenital or acquired enteric nervous system disorders.

Hirschsprung disease (HSCR) is a congenital anomaly of the colon that results from failure of enteric nervous system formation, leading to a constricted dysfunctional segment of the colon with variable lengths, and necessitating surgical intervention. The underlying pathophysiology includes a defect in neural crest cells migration, proliferation and differentiation, which are partially explained by identified genetic and epigenetic alterations. Despite the high success rate of the curative surgeries, they are associated with significant adverse outcomes such as enterocolitis, fecal soiling, and chronic constipation. In addition, some patients suffer from extensive lethal variants of the disease, all of which justify the need for an alternative cure. During the last 5 years, there has been considerable progress in HSCR stem cell-based therapy research. However, many major issues remain unsolved. This review will provide concise background information on HSCR, outline the future approaches of stem cell-based HSCR therapy, review recent key publications, discuss technical and ethical challenges the field faces prior to clinical translation, and tackle such challenges by proposing solutions and evaluating existing approaches to progress further.

CONCLUSIONS AND FUTURE DIRECTIONS

Since the clinical presentations by Harald Hirschsprung in Berlin in 1886, the condition that bears his name has had a rich history. The seminal events that influenced progress in the understanding and management of this complex congenital disorder have been briefly covered in this historical review. More than 100 years ago, the condition was considered incurable and uniformly fatal over time (12, 13). Mortality rates continued to be high in the 1940s (70%) and remained high even in the 1970s (25%). By the 1990s, more than 90% of patients survived (14).

Currently, the survival in most ad-
vanced medical environments is greater than 95%, excluding cases with chromosomal disorders or advanced comorbidities. While mortality has improved, there remains much to be learned. Why some patients with HSCR do poorly following operative repair remains an enigma. Similarly, the proper management of many patients with variants of HSCR needs to be more clearly elucidated. Continuing studies of the ENS and the molecular genetics of these conditions may shed further light on these issues and provide a better understanding of the choice of management in the future for affected children. Recent studies have transplanted human enteric neural progenitors into the mouse colon and shown engraftment (15). Currently, researchers are working to develop novel stem cell therapies, whereby stem cells could be transplanted into the aganglionic segment of bowel to replace the missing ENS.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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