SQU Med J, February 2011, Vol. 11, Iss. 1, pp. 138-145, Epub. 12th Feb 11

Hirschsprung's Disease Scientific Update

Sultan Qaboos University Hospital

25th October 2010

المعلومات العلمية الحديثة لمرض هيرشسبرنك

مستشفى جامعة السلطان قابوس، عُمان

25 أكتوبر 2010

Introduction to the Update and to Hirschsprung's Disease

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Hirschsprung disease (HSCR) is a developmental disorder of the enteric nervous system, characterised by an absence of ganglion cells in the distal colon resulting in a functional obstruction.[1] Although this condition was described by Ruysch in 1691 and popularised by Hirschsprung in 1886, Swenson in 1949 described the first consistent definitive procedure for HSCR.

Early diagnosis of HSCR is important to prevent failure to thrive, enetrocolitis, colonic perforation and dilatation of distal gut, which not only affects the type and number of surgical procedures, but also helps to prevent post-surgical morbidity. Patients need to be monitored closely after surgery for years after surgical treatment of HSCR. With early diagnosis and timely treatment, most children with HSCR will not have long-term adverse effects and can live normally.

Our observation has been that there is paucity of the knowledge about HSCR in our region. This observation has been based on the late referral of children with chronic constipation from primary health care teams to tertiary hospitals in Oman. The diagnosis of HSCR has been a dilemma due to many constraints. The management has been hampered both by local beliefs and by inadequate community and parental education about the impact of delaying surgical treatment in these children. The result is poor outcome with or without surgical intervention and hence the cycle goes on. To address this complex socio-medical issue, we organised this educational session for general doctors, nurses and specialists, who are involved in care of children, to highlight the necessity of early referral, diagnosis and the management.

Currently, approximately 90% of patients with HSCR are diagnosed in the newborn period.[2] HSCR should be considered in any newborn, who fails to pass meconium within 24–48 hours after birth, or in any child with a history of chronic constipation since birth. Other symptoms include bowel obstruction with bilious vomiting, abdominal distention, poor feeding, failure to thrive and poor weight gain as shown in Figure 1 below. The exact worldwide frequency of HSCR is unknown, but reported occurrence is approximately 1:1500–1:7000 newborns.[3,4] HSCR occur more often in males; however, long-segment disease is common

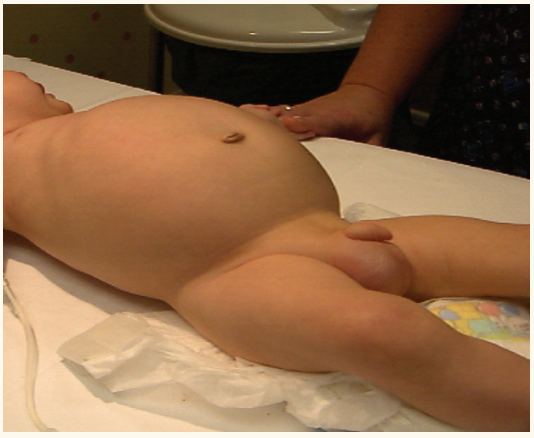

Figure 1: Hirschsprung's disease patient with abdominal distension and visible bowel loops.

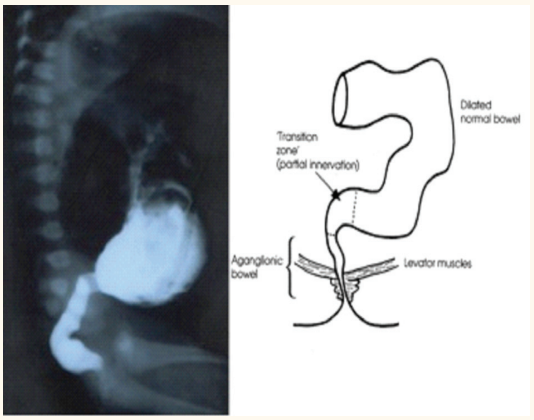

Figure 2: Barium enema of Hirschsprung's disease patient showing narrow rectosigmoid with proximally dilated bowel. The drawing is a demonstration of the radiological findings.

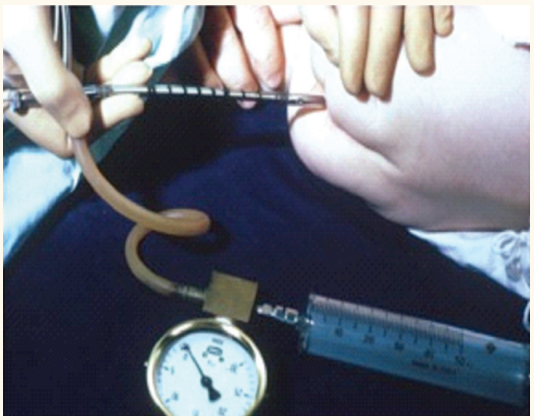

Figure 3: Suction rectal biopsy procedure for patients with suspected Hirschsprung's disease.

in females. HSCR is uncommon in premature infants. Approximately 20% of infants will have one or more associated abnormalities involving the neurological, cardiovascular, urological, or gastrointestinal systems.[5]

Children may present with diarrhoea caused by enterocolitis, which is related to stasis and bacterial overgrowth. This may progress to colonic perforation, causing life-threatening sepsis.[6] Plain abdominal radiographs may show distended bowel loops with a paucity of air in the rectum. A barium enema will demonstrate a narrowed distal colon with proximal dilation, a classic finding of HSCR, [Figure 2]. Another positive radiographic finding of HSCR is the retention of barium for longer than 24 hours after the barium enema has been performed. Anorectal manometry, which detects the relaxation reflex of the internal sphincter after distension of the rectal lumen and this normal inhibitory reflex is thought to be absent in patients with HSCR, is not commonly used for HSCR due false positive results and other limitations.[7]

The gold standard to diagnose HSCR is rectal biopsy. The current practice is to perform a bedside simple suction rectal biopsy in the newborn to obtain tissue for histologic examination by a special device [Figure 3]. On histology, both the myenteric (Auerbach) plexus and the submucosal (Meissner) plexus are absent from the muscular layer of the bowel wall and hypertrophied nerve trunks enhanced with acetylcholinesterase stain are also observed throughout the lamina propria and muscularis propria.

Once the diagnosis is confirmed, the treatment is to remove the poorly functioning aganglionic bowel [Figure 4] and to create an anastomosis to the distal rectum with the healthy innervated bowel (with or without an initial diversion). A number of definitive procedures have been used, all of which have demonstrated excellent results in experienced hands. The three most commonly performed surgeries are the Swenson, Duhamel, and Soave endorectal pull-through procedures. Recently, the transanal pull-through in which no intra-abdominal dissection is performed has also been popular.[8,9] Another addition to the surgical armamentarium is the laparoscopic approach to the surgical treatment of HSCR,[10] where the transition

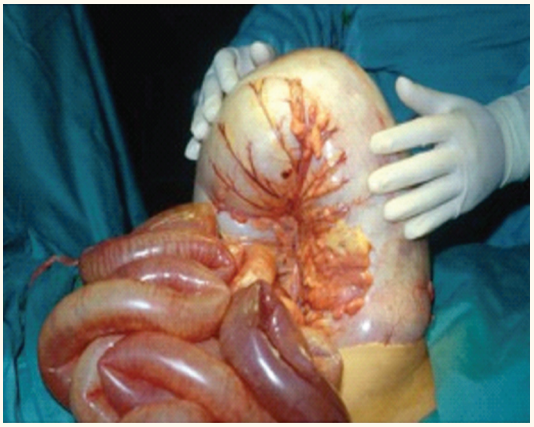

Figure 4: Operative findings in a Hirschsprung's disease patient showing hugely dilated distal gut proximal to the aganglionic segment of bowel.

zone is first identified laparoscopically, and then the mobilised rectum is brought down through the anus. Short-term outcomes for both, transanal and laparoscopic approaches have been similar to open single stage approaches with the benefits of minimal analgesia and shortened hospital stays.[8,11,12] Postoperatively, although patients may encounter one or more problems such as anastomotic leak, anastomotic stricture, intestinal obstruction, pelvic abscess, wound infection, chronic constipation, incontinence and enterocolitis, the long-term follow-up studies have shown that greater than 90% of children experience significant improvement and will do relatively well.[8,11,12] Patients with an associated syndrome have been found to have poorer outcomes.[13,14]

The future of children with HSCR is looking promising. The possibility of stem cell transplantation into the aganglionic gut and the reactivation of dormant stem cells in the gut to regenerate the enteric nervous system are being actively investigated.[15] Experiments have demonstrated that neural crest stem cells (NCSC) are present, even in the adult gut, and are capable of proliferation and differentiation. In addition, researchers have been able to inject neural crest stem cells and later identify them in the native rectum. Whether or not injected stem cells or reactivated native progenitor cells will have the capability to recreate a functional enteric nervous system remains to be elucidated.

SPECIAL CONCERNS

Total colonic aganglionosis is a more severe form of HSCR in which the entire colon and even some of the small intestine is aganglionic. These children have increased morbidity and mortality.[16,17] Ultrashort-segment HSCR is characterised by a few centimeters of aganglionic bowel in the rectum, adjacent to the anus. Recognizing this condition can be very difficult. These patients are not typically diagnosed until they are older and most patients can be satisfactorily treated with a surgical myomectomy, which involves resecting a longitudinal strip of the posterior muscular wall of the rectum.

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What is Hirschsprung Disease – A surgeon's perspective

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Hirschsprung's disease (HSCR) is a common cause of intestinal obstruction that affects 1:1500 to 1:5000 live births. It is more common in male children. It usually presents in the newborn period as intestinal obstruction or in older children as constipation and abdominal distention. HSCR occurs due to the absence of ganglion cells in the muscle wall at muscle and submucosa levels, hence causing a failure of relaxation of the circular muscle and internal sphincter, leading to functional constipation. It occurs in the rectosigmoid in 85% of cases; however, HSCR may be more extensive and may extend into the entire colon (total colonic HSCR). The diagnosis of HSCR is made by demonstration of absence of ganglion cells in the submucosa or in muscle layer of the intestine. A plain X-ray of the abdomen will show a distended bowel with no gas shadows in the pelvis. When a barium enema is done, it will delineate a dilated proximal colon and a very narrow "corkscrew" rectum. Rectal biopsy is performed after bowel decompression and the specimen is then subjected to a histopathological examination by the usual staining technology (haematoxylin and eosin) or enzymehistochemistry methods that demonstrate an abundance of acetyl cholinesterase (ACh) in the nerve bundles. Once diagnosis is confirmed, either a one-stage procedure involving resection of the aganglionic bowel and restoring continuity or a multi-stage procedure (colostomy, pull-through and reversal of stoma) is carried out. In patients who have failed to achieve good decompression of the proximal bowel or in whom there is refractory enterocolitis, a preliminary diverting colostomy is mandatory. There are quite a few techniques to perform definitive (pull-through) procedure in HSCR and the recent development is minimal invasive surgery. Irrespective of the type of surgery technique, the outcome is promising and fairly good long term results are achieved in over 85% cases. Constipation and/or occasional soiling have been noted in about 15% of children in the post-operative period. One of the most serious early complications is anastomotic leak and intestinal obstruction and the most serious late complication is enterocolitis. Enterocolitis in HSCR can be serious and life threatening, hence it is addressed very aggressively and has been seen more often in patients who have had enterocolitis prior to definitive treatment or those in whom there has been persistent obstruction. It is possible to do re-surgery in patients who have had inadequate results or in those whose colon becomes much dilated due to inadequate post-operative bowel management. The role of parents, patient and community nurses in ensuring good regular evacuation cannot be overemphasised.

Medical Aspects of Hirschsprung's Disease

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This paper includes a brief introduction about the history of Hirschsprung disease (HSCR), as well as an introduction to its pathogenesis and epidemiology as described in the literature. The typical clinical manifestation of HSCR might not be evident in all patients, which poses major difficulties in diagnosing children with atypical features of HSCR and therefore delays its treatment. Criteria for the diagnosis of HSCR in different age groups is discussed with proposal of an algorithm for patients with delayed passage of meconium according to their accessibility to medical care and opportunities for close follow-up in the Omani health system. The different presentations of HSCR are explained and studies of differences between children with idiopathic constipation and children with constipation secondary to HSCR. These studies did not show major differences in the clinical features based only on constipation, once again making it even more difficult to identifying HSCR based solely on clinical features without further investigations. The only exception is a child with constipation with no other organic features, normal natal history, normal growth with normal physical examination and normal rectal examination. To most pediatricians, this presentation is not commonly seen in Oman. Very few children with a history of constipation, who are referred to us at the pediatric gastroenterology unit of Child Health Department at Sultan Qaboos University Hospital, have this negative history and physical examination. Studies comparing diagnostic investigations commonly used for HSCR have revealed significant differences in the sensitivity and specificity of such investigations. Suction rectal biopsy (SRB) and anorectal manometry (ARM) (when the expertise is available) have the highest sensitivity and specificity. SRB and ARM are therefore preferred over contrast studies if HSCR is to be ruled out with greater certainty. HSCR is not a disorder seen in children only. Different age groups (including adults) can have HSCR, with interesting studies comparing the initial presentation, different pathogenesis and outcome in older patients compared to children. Case reports describe adults with long standing constipation to have catastrophic complications with enterocolitis and gut perforation found on postmortem examination. Adults with long standing constipation should be investigated for HSCR. Hirschsprung's associated enterocolitis (HAEC) is a known major complication of HSCR. The discussion covers it definition, pathogenesis, when to suspect it and how to diagnose and treat it as a pediatrician (and not a surgeon). Appropriate and timely medical intervention avoids morbidity and mortality from HAEC.

Hirschsprung's Disease and Syndromes

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Hirschsprung's disease (HSCR) is an important genetic cause of functional intestinal obstruction. About 20% of HSCR cases have another congenital anomaly either isolated or part of a syndrome (mainly monogenic Mendelian inherited). HSCR is a congenital malformation of the hindgut, a neurocristopathy, resulting from failure of migration of the neural crest cells that form the enteric nervous system between 5–12 wks gestation. Neurocristopathies are a group of diverse disorders resulting from defective growth, differentiation, and migration of the neural crest cells. Neural crest is a multipotent embryonic structure that gives rise to neuronal, endocrine and

paraendocrine craniofacial, conotruncal heart and pigmentary tissues.Here we present a few examples of syndromic HSCR. HSCR is frequently associated with syndromic neurocristopathy disorders such as Shah-Waardenburg syndromes (WS4), a clinically and genetically heterogeneous disorder characterised by pigmentary anomalies of the hair, skin and iris and sensorineural deafness and a long segment HSCR.WS4 is caused by homozygous mutations in EDNRB (AR) or heterozygous SOX10 mutations (AD). Another example of a neurocristopathy disorder is Haddad syndrome - defined by an association of HSCR and congenital central hypoventilation syndrome due to PHOX2B gene. Most cases are sporadic and few are dominantly inherited. Screening for other neurocristopathy tumours such as neuroblastoma may be indicated. The syndromic HSCR, commonly associated with dysmorphism, is the Mowat-Wilson syndrome, associated with HSCR in 60% of cases. These patients have a characteristic facial gestalt with multiple congenital anomalies and severe mental retardation. It is caused by heterozygous de novo deletions encompassing the ZEB2 or truncating mutations. HSCR is also frequently associated with a wide spectrum of additional isolated anomalies such as hypospadia, limb abnormalities, cardiac atrial septal defect (ASD) and ventricular septal defect (VSD). All HSCR patients should be carefully evaluated for additional anomalies.

Embryological and Molecular Mechanisms of Hindgut and Enteric Nervous System Development

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Hirschsprung disease (HSCR) and anorectal malformations result from alterations in hindgut development. Progress in the understanding of the genetic basis of HSCR and other anorectal malformations has been made by the application of the findings from genetic and chemical animal models of altered hindgut and neuromuscular development. Several genes have been shown to be important for the hindgut and enteric nervous system development and work is going on to identify genetic alterations and interactions that may explain the variable phenotypes of HSCR and ARMs. We used ethylenethiourea (ETU) rat model in our lab to study the embryological and molecular mechanisms of hindgut and enteric nervous system development. Our experiments have shown that the downregulation of shh, BMP4 and hox genes in developing hindgut of ETU-exposed fetal rats. When the immunohistochemical studies of the neurons and glia that comprise the enteric nervous system (ENS) (the intrinsic innervations of the gut) were performed, we found that there was marked reduction in the immunoreactivity of NSE, VIP and SP in the hindgut of experimental foetuses as compared with the controls. Our observations are that the expression of shh and its target genes in ETU-exposed fetal rats is downregulated and intramural nerves, stained by VIP and SP-100 antisera, were decreased in various phenotypes of hindgut developmental derivatives. The embryological and cellular mechanisms of hindgut development in ETU-exposed fetal rats will be presented as well as similar work done in other laboratories.

Current Molecular Biological Understanding of Hirschsprung's Disease

Dr. David Croaker

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People have appreciated the hereditary contribution to Hirschsprung's (HSCR) disease at least since the 1960s. At about the same time, the association with Down syndrome was noted. Since then, particularly in the last 20 years, a number of karyotype abnormalities have been observed on a number of chromosomes. The observation of an interstitial deletion on chromosome 10 about 20 years ago was an important clue to the identification of the first and most important gene responsible for Hirschsprung's disease-RET. At the same time gene screening for mutations in this gene never identified more than a minority of patients with significant sequence changes in the coding region. It became apparent that HSCR risk was determined by the sum of a number of risk alleles, as well as, more rarely, by mutations of large effect in RET and also other genes, such as the endothelin B receptor gene. There are about a dozen relatively important genes, and perhaps many dozens more less important genes, contributing to HSCR. Some of these genes are associated with particular and recognisable phenotypes, such as the so-called Mowat-Wilson syndrome described by us. Other gene mutations carry implications that are not necessarily immediately obvious: some mutations in Phox2b for instance carry a risk of neuroblastoma. Particular mutations in RET are responsible for multiple endocrine neoplasia type 2 (MEN2) cancer syndromes. It is of interest that a long-term follow-up in Scandinavia has picked up a higher rate of medullary thyroid cancer in adult survivors of Hirschsprung's disease. Although I do not believe that gene therapy will even be possible in the majority of cases, gene screening for known multi-case families is certainly possible, and may be useful, particularly as the cost of sequencing comes down. In particular, mutation screening would be of some use if it detects that minority of patients who may be at risk for malignancy, or other as yet undiscovered late effects. We already screen RET for several of the known MEN associated mutations in Hirschsprung's patients on occasion. At present, we are studying the lethal spotting rat, a Hirschsprung's disease model with a mutation in the endothelin B receptor gene, and a phenotype like the Shah-Waardenburg syndrome in humans. This animal suggests clues as to where our attention should be directed in further human studies and follow-up.

Anorectal Manometry in Hirschsprung's Disease

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Hirschsprung's Disease (HSCR) is a common intestinal anomaly that presents mainly in the neonatal age. The diagnosis may prove difficult in patients with no classical symptoms. The gold standard of diagnosis remains rectal biopsy. Anorectal manometry (ARM)

relies on absence of recto-anal inhibitory reflex. The test is infrequently done due to the absence of standardised reference ranges and high false negative rates. However, recent studies in neonates have shown reliable results. ARM is being further developed and might have wider diagnostic use in the future. ARM has an important role in assessing postsurgical patients with HSCR to determine the integrity of the anal sphincter. ARM has helped in planning the management of patients with both constipation and incontinence post surgery.

Radiological Findings of Hirschsprung's Disease

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Radiology in HSCR is paramount as it helps the clinicians to make the diagnosis as well as to evaluate postoperative morbidity. This presentation addresses the following. 1) Imaging Protocol: plain radiography; single-supine view; two views - frontal and left lateral decubitus or upright or crosstable view; contrast enema; 2) Contrast media: water soluble contrast enema or barium enema; 3) Preparation and technique; 4) Imaging findings: radiography - multiple dilated bowel loops and paucity of air in rectum; contrast enema- recto-sigmoid ratio <1; presence of narrowed zone (transition zone); fasciculation or saw tooth appearance of mucosa of involved colon; delayed emptying of contrast media from colon; thickened ulcerated colon if associated with enterocolitis; normal study in early weeks; 5) Classification criteria: short segment - 70–80% cases; long segment - 15–25% cases; total colonic - 1–4% cases; ultra short segment - rare; 6) Differential diagnosis: meconium plug syndrome; meconium ileus; immature colon; ileal atresia; colonic atresia.

Pathological Findings in Hirschsprung's Disease

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Hirschsprung's Disease (HSCR) is a group of disorders characterised by a lack of propulsive peristalsis in the distal colon resulting from an absence of ganglion cells in the wall (submucosal and myenteric). An increase in adrenergic and cholinergic nerves is associated in the aganglionic segment. Colonic smooth muscle relaxation is also deficient due to the disturbed function of vasoactive intestinal polypeptide and nitrous oxide mediated inhibitory nerves. The HSCR can be of short or long segment type, total bowel aganglionosis, ultra-short segment HSCR and zonal aganglionosis. Diagnostic work up requires a full-thickness rectal biopsy specimen for haematoxylin and eosin staining and various special stainings. Inadequate tissue samples and low rectal biopsy are major pitfalls for histopathology. Pathologic diagnosis includes pre-operative and intra-operative biopsies. The presence of ganglion cells in rectal or colonic biopsy rules out the possibility of HSCR. Multiple serial sections need to be examined before a definitive diagnosis of HSCR can be rendered. The special stainings such as acetylecholinestrase staining, calretinin immunostaining and rapid intra-operative immunoperoxidase staining for synaptophysin have been found to diagnose HSCR much faster and more accurately. In Hirschsprung associated enterocolitis (HAEC), microscopic examination reveals cryptitis, crypt abscesses, mucosal necrosis and transmural necrotising inflammation and perforation. The co-existence of neuronal intestinal dysplasia (NID) above the aganglionic segment of HSCR can complicate the interpretation of intra-operative biopsies specimen for HSCR. The diagnosis of intestinal motility disorders remains a challenge for both clinicians and pathologists.

Difficulties in Hirschsprung's Disease Pathology

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Hirschsprung's disease is characterised histopathologically by demonstrating aganglionosis in the Meissner (submucosal) and/or Auerbach (myenteric) plexuses of the rectum, depending on whether the specimen is mucosal or full thickness. Equally important for patient management is establishing the presence of ganglion cells in the proximal functional colonic segment at the anastomotic site after surgical resection of the aganglionic segment. Factors that render histopathologic diagnosis difficult in both these settings include: site (sampling: operator dependant) and type of biopsy (rectal suction vs. full thickness); type of histopathologic processing (frozen vs. paraffin); nature of disease (classical vs. ultrashort segment vs. total colonic aganglionosis); abnormal appearance of ganglion cells or poor development (neonates) and their look-alikes; availability and standardisation of adjunctive techniques (histochemistry and immunohistochemistry); differential diagnosis like functional constipation, hypoganglionosis, intestinal neuronal dysplasia, pseudo-HSCR and, lastly, familiarity with morphologic patterns (observer dependant). False positive and false negative diagnosis based on these factors impact clinico-pathologic correlation thus affecting patient management.

Current Surgical Management of Hirschsprung's Disease

Dr. Adel Ismail

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Hirschpsrung's disease is a common cause of intestinal obstruction in children and requires surgical intervention, where the surgeon removes the aganglionic part of distal gut and restores the continuity. The surgical treatment of this condition has gone through various stages of the development. Initial surgical management was multi-stage, where the surgeon would create a colostomy to relieve the

obstruction, later resect the aganglionic bowel and do a pull-through procedure and finally the reversal of stoma. This traditional approach has changed and progressed to an entirely transanal pull-through procedure, where the entire operation is performed without laparotomy. This paper presents a brief review of the various surgical procedures used for the treatment of HSCR and the impact of the transanal procedure on the management HSCR in various age groups.

Long term Outcome of Hirschprung's Disease – Oman experience

Dr. M. Jaffer Sajwani and Dr. Lalith Wijesinghe

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The surgical management of Hirshcsprung's disease (HSCR) has progressed, over the last few decades, from a 2–3 staged procedure to a primary operation. In the past decade, definitive surgery for the HSCR has been performed using minimally invasive techniques. We have been operating on HSCR children for the last 25 years and here share our recent experience. In the period 2001–2009, we operated on 85 children with HSCR and have been able to collect follow-up clinical data regarding functional outcomes for 79 children. Follow-ups were divided into the type of pull-through, age at time of procedure and length of the last follow-up. Follow-up periods ranged from 1 month to 8 years. We employed different operative procedures for HSCR: Duhamel in 50, Soave in 23, Swenson in 2 and the transanal procedure in 10 children. Post-operative complications included enterocolitis (10%) and bowel obstruction secondary to post-op adhesions (10%). There was no mortality. Post-operatively, constipation was observed more in children who underwent the Duhamel procedure, when compared with other groups. Functional outcomes were not significantly different among the various operative techniques.

Long term Outcome of Hirschsprung's Disease – Dubai experience

Dr. A. R. Mustafawi

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Over the last hundred years, different surgical techniques have been used for definite correction of Hirschsprung's disease (HSCR) in multi-stage procedures. Now the transanal endorectal pull-through has become the standard surgical procedure fro HSCR. Since March 2004, our protocol for HSCR is to proceed for single stage transanal pullthrough in the same anaesthesia session after rectal biopsy frozen sections have proved HSCR positive. During the period 2004 to date, 68 patients have been diagnosed with HSCR and all except 7 patients have been treated by single stage endorectal pull-through. We share our results and the follow-up of these patients. We believe that our protocol for HSCR is a real single-stage transanal pull-through as it avoids two general anaesthesias, is cost-effective and facilitates a shorter stay in hospital with no more colostomies and associated morbidities.

Long term Outcome of Hirschsprung's Disease – Qatar experience

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We have been managing children with Hirschsprunt's disease (HSCR) in Qatar for many years and here I share our experience both of the modes of presentation and the outcomes of children with HSCR in the last 10 years. We have reviewed our experience of the different surgical techniques used for the care of these patients and draw attention to the impact of the transanal approach on the management of this condition. During these 10 years, we had 39 children diagnosed with HSCR. Seven children were managed by traditional 3-staged surgical procedure; three of them had total colonic aganglionsis. The remaining 32 children had one-stage pull-through, either assisted by laparoscopy or mini-laparotomy or the entirely transanal approach. Postoperative complications included enterocolitis (12.8%), stricture (7.6%), soiling (2.5%) and constipation (28%). The mean hospital stay was 12, 5 and 3 days for the staged procedure, one stage assisted procedure and transanal procedures respectively. One child died.

Long term Outcome of Hirschsprung's Disease – Canberra experience

Dr. David Croaker

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Looked at over the last 40 years, we can see that survival from Hirschsprung's disease has improved from about 70% in the 1960s, to close to 100% now. Not only has survival improved, but the mean age at diagnosis has also improved, and plateaued about 20 years ago. I will discuss results first presented during my Ph.D. more than 10 years ago, then some results presented more recently after we started regularly to use laparoscopic assisted transanal pull-throughs, and give a roundup of my impression of the literature of the last few years. Generally speaking, functional results after pull-through are not quite as good as the older generation of surgeons liked to believe. There is a substantial incidence of at least some degree of soiling and constipation. Survival, however, has improved and modern laparoscopic surgery means that patients are subjected to much less surgical trauma and fewer operations with less time in hospital. I want to stress that long-term follow-up does not only include the functional results for defecation and continence, but also should include an assessment of general quality of life, psychological well-being, and the possibility of an increased risk of associated illnesses as foreshadowed in my talk on the genetics of Hirschsprung's disease. We do not know how our patients will do as they enter middle and old age. This knowledge requires decades of follow-up. Well-constructed studies of this sort are difficult to achieve, and there are few

of them in the literature. Hirschsprung's enterocolitis is still a poorly understood problem, and a source of much of our remaining post-operative morbidity. It may very well be multifactorial, and it has been suggested that Hirschsprung's disease patients may have immune deficits, altered motility and functional obstruction, or simply technical anastomotic problems giving them low-grade obstruction. All of these factors may then singly or in combination result in enterocolitis. Although in most cases the attacks decrease with age, while in some patients there are persistent problems. I will discuss several ideas concerning this entity. Several authors and research groups are investigating the possibility of stem cell rescue in the animal model. The development of the enteric nervous system is complex and guided by signals that are ordered in both space and time. It remains to be seen whether injected neuroblasts will be able to order themselves in a functionally useful way. If this sort of therapy is possible, it would make bowel resection and anastomosis a thing of the past. Despite the promise of the new genetic technologies, in practice progress at present is more evolutionary than revolutionary and good results continue to depend on attention to all the details of care.