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Long-term outcomes and quality of life in patients with Hirschsprung disease

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ABSTRACT

Although patients with Hirschsprung disease are mostly affected by imperfect bowel function and fecal control in the long term, they are also predisposed to lower urinary tract symptoms, impaired sexual functions, infertility, psychosocial issues, and decreased quality of life. Rare, but notable comorbidities, which may manifest after childhood, include inflammatory bowel disease and familial medullary thyroid cancer. Despite frequent occurrence of fecal incontinence and constipation, the overall long-term outlook is quite optimistic as social continence with a good quality of life can be achieved by efficient bowel management also in those affected patients, whose self-coping strategies and medical treatment remain insufficient. Bowel dysfunction and other potential long-term complications are best managed by an interdisciplinary specialized approach not overlooking psychosocial issues, which also helps to correctly identify areas requiring continuing input by adult healthcare for young adult patients after transition. Additional research is needed to unravel the pathophysiological mechanisms of the long-term bowel dysfunction to identify novel therapeutic targets for development of more efficient innovative management strategies and thereby improvement of quality of life.

INTRODUCTION

While aganglionic bowel can be safely removed with several well-established surgical techniques, it has become increasingly evident that a significant proportion of patients with Hirschsprung disease (HSCR) suffer from long-term postoperative morbidities not entirely limited to bowel dysfunction.[1–5] Thus, both involved medical professionals and patient representatives have shifted their interest to long-term sequela of HSCR variably affecting bowel, lower urinary tract and sexual function, fertility, psychosocial well-being, and ultimately quality of life during childhood and in adulthood (table 1). While many of these long-term problems appear causally connected with each other and tend to cluster in certain individuals, their severity also depends on the length of aganglionosis and associated syndromes.[3 4] The underlying genetic defect causing HSCR may also predispose to other disorders later in life, such as medullary thyroid carcinoma, whereas increasingly encountered HSCR-associated inflammatory bowel disease (IBD) remains inadequately characterized with unclear pathophysiology.[6–8] Disturbances in bowel function and fecal control predominate the first years following surgery but persist, although to a lesser degree, to adolescence and adulthood.[1 3 9] However, the overall long-term outlook seems quite optimistic as social continence with a good quality of life can be achieved by efficient bowel management also in those affected patients whose medical treatment and self-coping strategies remain insufficient.[1 3] Bowel dysfunction and other potential long-term complications are best managed by an interdisciplinary specialized approach not overlooking psychosocial issues, which also helps to correctly identify areas requiring continuing input by adult healthcare for young adult patients.[4] In this review, we present long-term outcomes of HSCR with a special emphasis to the period of reaching young adulthood.

BOWEL DYSFUNCTION

Rectosigmoid aganglionosis

Despite successful removal of the aganglionic segment, children with HSCR are at risk for long-term complications affecting bowel function following surgery, including fecal incontinence, obstructive symptoms or constipation, and Hirschsprung-associated enterocolitis (HAEC).[1–4 9]

Following pull-through surgery for HSCR, typical long-lasting manifestations of impaired bowel control include difficulties to recognize the need to defecate and fecal soiling, while fecal accidents occur less frequently.[1 2 4 9 10] Fecal soiling, escape of small amounts of liquid or soft stool, is a common long-term complication affecting up to 50% of adult patients after surgery for HSCR.[1 3 5 9 11 12] Fecal soiling often associates with increased defecation frequency especially after endorectal pull-through due to active propulsive peristalsis in the pulled through bowel transversing to the anus in

Table 1 Checklist for assessment of young adults with (rectosigmoid) Hirschsprung disease

Fecal incontinence and constipation	Assess the degree and social magnitudes of fecal incontinence and/or constipation, plan required investigations/interventions, optimize dietary and medical management, and support self-coping by providing information.
IBD-like symptoms	Screening of intestinal mucosal inflammation with fecal calprotectin before proceeding to endoscopy in patients with recurrent abdominal pain, diarrhea, bloody stools, or fever.
Lower urinary tract symptoms	Urinary flowmetry with ultrasound examination to rule out significant bladder dysfunction.
Sexual function and fertility	Erectile and ejaculatory function questionnaire/gynecologist consultation.
Social limitations	Psychosocial support.
Quality of life	Provide comprehensive patient information and preplanned structured transition of care as needed while avoiding overmedicalization.
Risk of medullary thyroid carcinoma	Consider genetic screening according to local practice.

IBD, inflammatory bowel disease.

the absence of a normal rectum to serve as a fecal reservoir.[13–15] The absence of rectal reservoir in combination with variably impaired sphincter performance and anal canal sensation may result in fecal soiling.[13 15] True incontinence, with the inability to hold back defecation, is due to insufficient anorectal sensory and/or sphincter function and is treated with bowel management or a diverting enterostomy.[16] In contrast, patients with fecal impaction with resulting overflow incontinence should be considered in the category of obstructive symptoms and approached as described below.[15 16]

Different aspects of bowel control including prevalence and severity of fecal soiling seem to improve along with age by adulthood,[1 3 9 10] although improvement of fecal soiling was not observed in a longitudinal assessment of the same patients at median age of 7.7 and 15 years.[17] Among young adults (age ≥18 years), the patient-reported prevalence of fecal soiling and accidents after endorectal pull-through were comparable to general population.[1] Still, around 10% of adult patients reported more problematic fecal soiling, occurring at least weekly or requiring use of protective aids, while less than 25% of patients reported any occurrence of fecal accidents.[2 5 9 12] In a large Dutch study including 346 patients, prevalence of any type of fecal incontinence, including fecal soiling, was 65% in pediatric and 29% in adult (age ≥18 years) patients, clearly exceeding the prevalence of normal population controls.[10]

Obstructive symptoms refer to severe difficulty evacuating typically associated with abdominal distension.[4 15 18] Although being relatively common during the first years of life, obstructive symptoms are rarely encountered as such beyond childhood unlike constipation.[13 15 18] Among adults, constipation occurs in 30%–40% of patients following Duhamel pull-through but only rarely after endorectal pull-through.[1–3 5 9 10 12] However, in relation to normal controls, the overall constipation prevalence of 38% was not significantly higher among adult patients, who had mostly undergone Duhamel or Rehbein reconstruction.[10] Multiple overlapping factors may cause obstructive defecation and constipation following a pull-through. Mechanical reasons include mainly surgical complications such as anastomotic stricture, twisting of the pull-through and a tight muscular cuff following endorectal pull-through or rectal spur after a Duhamel pull-through. Neural causes include persistently abnormal innervation of the internal anal sphincter with absent rectoanal inhibitory reflex and deficient relaxation, and colonic dysmotility secondary to abnormal enteric innervation of the seemingly normal ganglionated bowel even after adequate pull-through surgery, and a transition zone pull-through, in which the abnormally innervated transition zone was not inadvertently removed.[15 18–20] A thorough evaluation of a patient with obstructive symptoms or severe constipation includes anorectal examination, endoscopy, contrast enema, repeat rectal biopsy, anorectal manometry, and colonic manometry. The aim is to establish the underlying pathology for a targeted treatment strategy.[15 19 21]

Depending on the definition, up to 50% of patients experience HAEC at some point after endorectal pull-through.[4 21] However, apart from patients with total colonic aganglionosis (TCA), most enterocolitis episodes are encountered during the first years after the surgery before school age and become exceptional after puberty.[1 22 23]

Although overall long-term bowel function outcomes seem comparable after endorectal pull-through and Duhamel, some procedure-related differences exist.[12] HAEC episodes are over twice as frequent and stooling frequency remains persistently elevated after endorectal pull-through in contrast to Duhamel.[5 9 12 24] In addition to clearly higher prevalence of constipation, defects in fecal control may also be slightly more frequent in adults who

have undergone Duhamel pull-through likely related to fecal impaction and overflow in aganglionic rectal pouch.[12]

Extended aganglionosis

In relation to a shorter segment disease, TCA carries markedly more challenging outlook in the long term related to bowel dysfunction and other associated morbidity, and these patients in particular benefit from close individualized multidisciplinary follow-up also in adulthood.[25 26] With increasing length of small intestinal aganglionosis, greater attention to diarrhea, growth and nutritional issues is required.[22] Patients with near total or total intestinal aganglionosis should be followed up by an intestinal failure unit as they require prolonged or permanent parenteral nutrition and may benefit from complex intestinal reconstructive procedures or even intestinal transplantation.[22 23 26–28]

In addition to obstructive symptoms, TCA predisposes to more severe and recurrent HAEC episodes, which can localize in the unused bowel distal to a diverting enterostomy, supporting timely removal of the excluded aganglionic bowel.[23 29–32] A nationwide Swedish study reported 31% prevalence of obstructive symptoms in patients with TCA at median age of 10 years.[33] A greater loss of bowel including a variable segment of the distal ileum with accelerated intestinal transit and decreased fluid absorption leads to frequent loose stools further increasing the possibility of fecal soiling and incontinence.[34] Overall, 30%–80% of older children or adolescents with TCA suffered from different degrees of fecal incontinence.[35–38]

Duhamel and straight ileoanal anastomosis are the mostly used surgical techniques for TCA with no major differences in functional outcomes other than a lower stooling frequency after Duhamel.[22 39] While ileoanal anastomosis with J-pouch has provided promising functional results, further studies are needed to clarify whether inclusion of J-pouch increases the likelihood of obstructive symptoms with associated HAEC.[26 40 41]

Syndromic Hirschsprung disease

Genetic syndromes are frequently (12%) observed in patients with HSCR.[4] Their presence may negatively affect functional prognosis due to associated learning disability or consequences of the underlying genetic mutation. Patients with syndromic HSCR with a learning disability due to Down syndrome and Mowat-Wilson syndrome have markedly inferior functional outcomes, reflected by clearly reduced chances to achieve fecal and urinary continence and increased need for permanent stoma (>20% of patients) with significant impact on long-term quality of life.[9 42 43] These patients tend to attain bowel control much slower, and a higher proportion of them, especially those with recurrent enterocolitis, suffer from fecal incontinence as adolescents and adults.[13] Patients with cartilage-hair hypoplasia are prone to severe recurrent HAEC episodes also after a pull-through possibly due to an incompletely characterized immunodeficiency caused by variants of the disease-causing *RMRP* gene.[44 45] They also exhibit a higher incidence of extended aganglionosis with a poor functional prognosis and an increased mortality rate.[44]

BOWEL MANAGEMENT

While majority of patients with HSCR achieve voluntary bowel movements and fecal continence, some patients suffer from deficient fecal control or obstructive symptoms in as much to require bowel management with regular colonic enemas given either transrectally (retrograde) or through laparoscopically exteriorized appendix or cecostomy (antegrade).[3 4] The priorities in bowel management of patients with HSCR are to secure age-appropriate fecal continence and management of bowel symptoms to enable participation in normal activities and social interactions.[21] Successful bowel management is based on tailoring diet, laxatives, other medical therapy and the type and frequency of enema, when needed, according to individual characteristics of each patient by closely observing the treatment response to each intervention.[46] In patients with constipation, once mechanical causes have been ruled out, different laxatives and fiber can be applied, whereas patients with hypermotility-induced fecal soiling may benefit from a constipating high-fiber diet and antimotility agents before proceeding to colonic enemas.[47] Obstructive symptoms due to non-relaxing internal sphincter may be treated with (repeated) botulinum toxin injections, which have largely replaced posterior myotomy/myectomy.[47–50] In obstructive non-responders, a high-resolution colonic manometry may guide performance of colonic resection or correct level of an enterostomy.[15]

In a population-based series, 8% of patients had received an appendicostomy for antegrade colonic enemas and 6% a diverting enterostomy, both procedures concentrating in syndromic patients with extended aganglionosis.[51] In some patients, colonic enemas may be needed only temporarily to support gradual development of spontaneous continence.[52] According to our institutional experience with endorectal pull-through, approximately one-quarter of patients with HSCR were able to stop using antegrade colonic enemas after gaining acceptable bowel control when approaching adolescence. In occasional patients with intractable fecal incontinence or bowel dysfunction resistant to other therapies, permanent diverting ostomy may be the best solution to improve quality of life.

GENITOURINARY MORBIDITY, SEXUAL FUNCTION AND FERTILITY

Although low rectal dissection predisposes to iatrogenic pelvic injuries, lower urinary tract and erectile function appear well preserved in majority of adolescent patients with HSCR after endorectal pull-through.[53 54] No significant differences in lower urinary tract symptoms either after Duhamel or endorectal pull-through in relation

to normal population controls were observed in adult patients with HSCR.[12] Any degree of erectile dysfunction was observed in 18% of adult males with median age of 30 years after Duhamel, while 4.3% reported any concerns with ejaculation.[55] Erectile dysfunction was associated with poor bowel function.[55] In one study, urinary flowmetry in a 21-year-old male revealed a bladder neck stricture.[56] Screening urinary flowmetry is a feasible way to rule out bladder dysfunction while erectile function should also be assessed before transition of care.[53 54]

A lower proportion of adolescent female patients reported currently having a stable relationship in relation to normal population controls.[53] Moreover, adult female patients with median age of 29 years reported decreased sexual quality of life and difficulties to conceive spontaneously possibly related to postoperative pelvic adhesions.[57] In both sexes, sexual quality of life independently associated with poor bowel function.[57] Overall, these findings indicate that poor bowel function predisposes to impaired sexual quality of life, while a gynecologist consultation with information on possible fertility issues should be routinely offered to young adult females with HSCR.

OTHER COMORBIDITIES

An increasingly recognized yet poorly characterized long-term complication of HSCR is IBD. According to a population-based national registry study from Sweden, the risk of IBD in patients with HSCR was over fivefold higher than in general population.[7] Among the patients with confirmed IBD, 44% had been operated for rectosigmoid aganglionosis and IBD was classified as Crohn's disease in most.[8] Chronic intestinal inflammation and Crohn-like mucosal lesions (37%) seem particularly common in patients with TCA.[58] In a North American collaborative study, 71% of 55 patients with HSCR-IBD were classified as Crohn's disease and in 63% the diagnosis was made after age of 5 years.[59] Measurement of fecal calprotectin may be used as a screening tool for intestinal inflammation before proceeding to colonoscopy in patients with HSCR with clinical symptoms suggestive of IBD.[40 58]

Mutations of the *RET* proto-oncogene causing HSCR may also give rise to familiar medullary thyroid carcinoma (FMTC). In a Finnish study, the estimated prevalence of these activating FMTC/multiple endocrine neoplasia type 2A (MEN2A)-type mutations was around 5%, while two (1.3%) patients had developed FMTC at adult age.[6] Targeted genetic screening of FMTC/MEN2A-type *RET* mutations would enable prophylactic thyroidectomy for affected individuals.

QUALITY OF LIFE

Children with HSCR experience more physical, psychosocial, and overall quality of life problems compared with peers.[60 61] The effects of disease-specific symptoms, such as fecal incontinence or constipation, on quality of life vary between different study populations, while most studies indicate their central negative effect.[11 62–64] However, impaired psychosocial functioning appears to have even a stronger effect on quality of life than the disease-specific symptoms.[63 64]

According to different quality of life questionnaires, the overall scores are lower among adult patients with HSCR when compared with general background populations.[1 3 5 10] As expected, quality of life is mostly affected in patients with poor bowel functional outcomes.[3 5 12] Accordingly, effective treatment of fecal incontinence and constipation with a structured bowel management program improves quality of life.[46] Variable degrees of fecal incontinence or constipation persist into young adulthood.[3 5 9] The residual bowel dysfunction may bear a significant consequence on quality of life in young adult patients as diminished fecal control correlates highly with social, emotional, and sexual well-being.[3–5 57 65] Adolescent and adult patients report less bowel function problems than children but are more prone to quality of life problems.[5 63 66] Although bowel function often improves with age, some aspects of quality of life may not, possibly reflecting residual psychological burden from childhood or increasing social pressure in young adulthood.[65] Around 30% of adult patients report bowel symptoms impacting their social lives after endorectal pull-through.[2] Emotional distress and limited personal and sexual relationships negatively influence quality of life.[1 32 67] Adult patients with HSCR report a similar level of physical impairment in daily life as their healthy peers.[29 30] On the other hand, patients more often experience disordered mental health, including depression and anxiety, without significant associations with the disease severity or sex.[29–31] Of adolescent patients with HSCR, 22% fulfilled the criteria for psychiatric diagnosis which was more than in general population (15%). Long-term functional problems affecting bowel function, lower urinary tract symptoms and sexual issues appear to cluster with psychosocial problems resulting in poor overall quality of life in certain individuals.[3 57 65 68 69]

BECOMING YOUNG ADULT PATIENT

Patients with HSCR require close follow-up and collaborative interdisciplinary care throughout their childhood. While ensuring age-appropriate development and managing dysfunctional bowel symptoms, other possible comorbidities should be promptly addressed as well. Members of an interdisciplinary care team may include pediatric surgeon, gastroenterologist, nutritional therapist, psychologist, physiotherapist, specialist nurses and social workers.[21] The importance of supportive strategies to improve self-coping mechanisms and social integration cannot be overestimated, and psychosocial support should be readily available.[4]

As functional problems often persist into adulthood and correlate with social disability and decreased quality of life, particularly patients who continue to experience

significant social limitations highlight the need for robust transitional care arrangements (table 1).[70] Preplanned healthcare transition, patient empowerment by education of their condition and continuity of care improve the ability of young adult patients to manage their own condition and learn positive coping strategies, thereby optimizing long-term quality of life.[21 71] Unsuccessful transition of care, on the other hand, may have negative long-term implications on physical and mental health.[71]

CONCLUSION

Although outcomes of most patients with HSCR are encouraging, a minority of them and especially the ones with more extended aganglionosis suffer from significant long-term consequences of the disease. Many different aspects of psychosocial and quality of life issues are linked to suboptimal bowel function and fecal control, which necessitates continuation of care and supportive measures by interdisciplinary specialized approach also when patients with HSCR become young adults. Additional research is much needed to unravel the underlying pathophysiological mechanisms of the long-term bowel dysfunction to identify novel therapeutic targets for development of more efficient innovative management strategies and thereby improvement of quality of life.

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