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SEXUAL FUNCTION AND LOWER URINARY TRACT SYMPTOMS AFTER MINIMALLY
INVASIVE ENDORECTAL PULL-THROUGH IN ADOLESCENT MALES WITH
HIRSCHSPRUNG DISEASE

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Highlights

\begin{itemize}
  \item Knowledge about sexual function and the presence of lower urinary tract symptoms in Hirschsprung patients is very limited.
  
  \item Minimally invasive endorectal pull-through seems to preserve the ability to have an erection and to ejaculate in adolescent males. Lower urinary tract symptoms are rare.
\end{itemize}
ABSTRACT

Background: Effects of colorectal resection on sexual function and the lower urinary tract are inadequately studied in patients with Hirschsprung disease (HD). This study aimed to increase existing knowledge on sexual function and lower urinary tract symptoms (LUTS) in HD male adolescents operated with minimally invasive endorectal pull-through (ERPT).

Methods: Non-syndromic male adolescents (12-18 years) operated with ERPT were invited to participate in this single-center cross-sectional study which included a semi-structured interview on sexual function and LUTS, a questionnaire recording LUTS, and a urodynamic study. Uroflowmetry curves were eligible for evaluation if the voided volume was >50% of expected bladder capacity. Ethical approval and informed consent were obtained.

Results: Of 37 eligible male adolescents, 35 (95%) with a median age of 14.9 (12.0 - 18.3) years were included. 94% had rectosigmoid aganglionosis, and 97% underwent a minimally invasive ERPT. 34 (97%) visited the outpatient clinic. The ability to get erections and to ejaculate was assessed in 25/35 (71%) adolescents. 25/25 (100%) could get an erection, and of adolescents ≥15 years 14/15 (93%) could ejaculate. 32 (91%) returned the questionnaire and underwent urodynamic studies. 15/32 (47%) reported LUTS, but most had only sporadic LUTS. 31/32 (97%) were highly satisfied with their bladder function. Sporadic urinary incontinence was reported by 4/32 (13%), but none reported social problems due to this. Of the eligible 28/32 (88%) uroflowmetry curves, 15/28 (54%) were normal.

Conclusions: Minimally invasive ERPT seems to preserve sexual function and does not induce lower urinary tract symptoms in adolescent HD males.

Level of Evidence: III

Keywords

Hirschsprung disease; Endorectal pull-through; Minimally invasive surgery; Sexual function; Lower urinary tract symptoms; Adolescence

Abbreviations:
1. Introduction

Hirschsprung disease (HD) is a rare congenital disorder that is characterized by the absence of ganglion cells in the lower digestive tract predominantly affecting males [1]. Surgical management of HD involves removal of aganglionic bowel and restoration of bowel continuity. Rectal dissection is an integral part of any pull-through operation and has an inherent potential for injury to the urethra, bladder, ureters, sympathetic and parasympathetic lumbar nerves, prostate and spermatic cords in males and uterus, fallopian tubes, and ovaries in females. Damage to these structures may impair sexual function and induce lower urinary tract symptoms (LUTS) [2, 3]. There is very limited knowledge about sexual function and frequency of LUTS after surgical management of HD, and specifically after minimally invasive endorectal pull-through techniques (ERPT). A systematic review from 2016 on sexual function and/or LUTS in HD patients found that only 24 studies had been published during the last 40 years [4]. The majority of these studies reported results after open surgery and multi-staged procedures. Ten studies, including 624 males, had assessed erectile and/or ejaculatory function, and sexual impairment was very rarely reported [5-8]. In two more recent studies, sexual function was not different in 112 HD males and controls, while dyspareunia and subfertility were more frequent among 41 HD females compared to the
controls [9, 10]. In the above mentioned review, 17 studies including 2546 patients of both genders found that less than 4% reported any type of LUTS [11-14]. Four more recent studies present contradictory results regarding LUTS; some found no difference between HD patients and controls, whereas others reported that HD patients with impaired bowel function had more frequent LUTS than other HD patients [9, 15-17].

In addition to the paucity of studies examining sexual function and LUTS in HD patients, few studies have applied validated questionnaires or had an independent investigator interviewing patients and doing the chart reviews. Most studies are retrospective and based on chart reviews only. Furthermore, the age distribution of the patients often varies greatly, making it difficult to draw conclusions [4, 18-20]. Therefore, the aim of this study was to increase existing knowledge on sexual function and frequency of LUTS in HD male adolescents operated with minimally invasive ERPT by having an independent investigator interviewing the patients, applying a validated questionnaire and performing urodynamic studies.

2. Methods

2.1 Study design

This is a single-center cross-sectional study exploring sexual function and LUTS in male HD adolescents. Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were applied [21].

2.2 Surgical techniques, perioperative examinations and follow-up routines

Total transanal ERPT was performed mostly as described by de la Torre et al., but with a shorter mucosectomy [22, 23]. During laparoscopic assisted ERPT, the sigmoid colon and rectum were dissected down to the pelvic floor, and the mucosectomy was then performed transanally as in the total transanal technique.

There was no systematic screening for urinary tract for malformations. Investigations of the urinary tract had been done either because of urinary symptoms or because of prenatal findings. In addition, some had undergone abdominal ultrasound including examination of the
urinary tract before HD was diagnosed as a part of investigations for gastrointestinal symptoms.

Postoperative follow-up routines included frequent outpatient visits during the first year. Thereafter, frequency of out-patient visits depended on symptoms and availability for follow-up at the patients’ local hospital.

2.3 Ethics

Written informed consent was obtained from all adolescents ≥16 years and from parents of adolescents <16 years. Adolescents <16 years got age-adapted information about the study. The study was approved by the regional committee for medical and health research ethics (2018/2009) and the Hospital’s Data Protection Officer (18/19101). The study is registered in Clinical Trials (NCT04106947).

2.4 Patients, clinical setting and data collection

All non-intellectually impaired male adolescents (12-18 years), fluent in Norwegian, having undergone ERPT were eligible for inclusion. Patients were identified from the hospital’s electronic database and invited to participate by mail or during outpatient clinics.

Demographics, length of the aganglionic segment, investigations of the urinary tract, presence of hypospadias, and surgical details were recorded retrospectively from electronic medical records. Congenital anomalies of the kidney and urinary tract (CAKUT) was defined as renal agenesis, kidney hypoplasia, hydronephrosis, and/or vesicoureteral reflux [24].

To register current clinical status, the adolescents had a semi-structured interview at the outpatient clinic, a clinical investigation if indicated, and urodynamic studies. They were also asked to answer a questionnaire recording LUTS. This questionnaire was a 12-item modified version of the Danish Prostatic Symptom Score (DAN-PSS) (Appendix 1) [25]. LUTS was defined as one or more of the following symptoms: Voiding frequency >8/day, straining,
urgency, urge incontinence, stress incontinence, incontinence without physical activity/straining (passive incontinence), and bedwetting (enuresis). Those who did not want to attend the outpatient clinic, could participate in the study by only answering the questionnaire which was sent by post.

The semi-structured interviews were led by a surgeon who had not performed the ERPT operations or been responsible for the follow-up. The first part of the interview focused on current clinical status, including voiding habits and LUTS. All the adolescents were asked if they wanted to talk to the interviewer alone. If the adolescent and his parent(s) agreed, the interviewer talked with the adolescent alone from the age of 12. This was carried out as an informal conversation about sexual function. Sexual function was assessed by the adolescents’ self-reported ability to get erections and to ejaculate. Erection and ejaculation were reported dichotomously by the presence or absence of these functions.

2.5 Urodynamic studies

Uroflowmetry measuring flow rates and voiding volume was performed with the Flowstar Laborie/Medical Measurement Systems BV (MMS). Residual volume was measured by a suprapubic transcutaneous bladder scanning with the CUBEsca\nBioCon-700 by Mcube Technology. The uroflowmetry curves were considered reliable if the voided volume was >50% of expected bladder capacity [26]. The flowmetry curves were examined by two independent investigators (ATH, RAK), and if they disagreed, a third investigator (KB) was consulted. The flowmetry curves were classified as normal (bell-shaped) or abnormal (non-bell-shaped, plateau-, staccato- or interrupted shaped) [26].

2.6 Statistics

Continuous variables are presented as median (min-max). IBM SPSS software for Windows version 25 (Armonk, NY: IBM Corp.) was used.

3. Results

3.1 Adolescents
Of 41 identified adolescents who had undergone ERPT, four had intellectual impairment. Consequently, 37 adolescents were invited to participate. Two did not respond, and 35 (95%) adolescents with a median age of 14.9 (12.0-18.3) years were included. Thirty-four (97%) visited the outpatient clinic. Two (6%) had aganglionosis proximal to the rectosigmoid colon, and 34 (97%) were operated with minimally invasive techniques, either total transanal or laparoscopic assisted ERPT (Table 1). One adolescent had been operated abroad with laparotomy assisted ERPT, but follow up was done at our center. None of the patients had intraoperative urologic injury, postoperative anastomotic leakage or redo surgery.

3.2 Sexual function

Twenty-seven adolescents agreed to talk to the interviewer about sexual function, but two adolescents (12 years) did not understand the questions and were excluded. Thus, 25/35 (71%) adolescents, median 15.4 (12.4-18.3) years, could be assessed for sexual function. All of the 25 adolescents reported that they could get erections.

Eighteen of 25 (72%) adolescents, median 17.0 (13.3-18.3) years, told the interviewer that they could ejaculate. Of the adolescents ≥ 15 years, 14/15 (93%) could ejaculate. Seven adolescents, median 13.3 (12.4-15.9) years, knew they had not ejaculated. None of the adolescents reported retrograde ejaculation.

3.3 Urology

3.3.1 Investigations and operations in the urinary tract

Seventeen of 35 (49%) adolescents had undergone one or more previous investigation of the urinary tract. Fifteen (88%) had undergone ultrasound, four (24%) uroflowmetry and measurement of residual volume, three (18%) a micturating cystourethrogram (MCUG), two (12%) scintigraphy, and one (6%) a cystometry.

Ultrasound examinations had been normal in all but three. Findings in these three included unilateral hydronephrosis and hydroureter, unilateral hydroureter and a hypoplastic ipsilateral kidney, and isolated unilateral hydronephrosis. These three boys underwent further investigations. MCUG showed vesicoureteral reflux grade 3 and 4 in the two boys with
hydroureter. Scintigraphy was performed in the same two boys and showed in both significantly reduced function in the ipsilateral kidney. The boy with isolated hydronephrosis got a repeat ultrasound showing no hydronephrosis. Two boys with initial normal ultrasonographic findings later underwent MCUG due to epididymo-orchitis and daytime urinary incontinence, and they had vesicoureteral reflux grade 0 and 2, respectively. Thus, four boys had six CAKUT: Kidney hypoplasia (1), hydronephrosis (2), and vesicoureteral reflux (3). None of the adolescent males had previously been diagnosed with hypospadia.

Uroflowmetry and measurement of residual volume had been done previously in four boys because of neurologic disease without intellectual impairment, macroscopic hematuria and urinary tract infection, late onset bedwetting, and urinary hesitancy. Only the boy with a neurologic disease without intellectual impairment had a pathological uroflowmetry with large voided volumes, but no residual volumes. Cystometry in the same boy showed signs of a neurogenic bladder. Two boys underwent a urologic operation. Both had endoscopic Deflux®-injections due to vesicoureteral reflux.

3.3.2 Lower urinary tract symptoms (LUTS)

32/35 (91%) LUTS questionnaires were returned. 15/32 (47%) adolescents reported to have one or more LUTS, but the majority had only sporadic LUTS (Table 2). Urge, straining and any urinary incontinence occurred in 9/32 (28%), 8/32 (25%), and 4/32 (13%), respectively. None had bedwetting or social problems due to urinary incontinence. 31/32 (97%) adolescents reported high or excellent satisfaction with their bladder function. Low satisfaction with bladder function was noted in only one adolescent, and he had a neurologic disease without intellectual impairment.

3.3.3. Findings from urodynamic studies
Urodynamic studies were completed by 32/35 (91%) adolescents, but due to a technical problem only 31 curves could be evaluated. 28/31 (90%) had a voiding volume >50% of expected bladder capacity, and only the curves of these were examined (Table 3). The uroflowmetry curves were normal in 15/28 (54%). 7/28 (25%) had a plateau curve, 5/28 (18%) had a staccato curve, and 1/28 (4%) had an interrupted curve. 19/28 (68%) adolescents had a voided volume exceeding their expected bladder capacity. Of those with a plateau curve, all had a voided volume exceeding their expected bladder capacity.

3.4 Results from semi-structured interviews

The interviews with the adolescents and parents together lasted from 60 to 90 minutes, whereas the interviews with the adolescents alone lasted from 5 to 30 minutes. Generally, the length of the interview with the adolescents increased by increasing age of the adolescent (results not shown).

One of the first adolescents we interviewed, suggested that information regarding sexual function was not be reported in medical records available for the parents as this would make it easier to talk more freely. Subsequent adolescents were informed that data on sexual function would not be recorded in their medical records. None of the adolescents seemed to find it difficult or embarrassing to talk about sex, and they did not attempt to finish the conversation before it came to a natural ending. Several adolescents expressed concerns about the size and appearance of their penis. Furthermore, 3 (9%) adolescents attending the outpatient clinic had problems with phimosis. One was referred for surgical treatment, and two got conservative treatment.

During the semi-structured interview voiding habits were investigated further as a supplement to the questionnaire on LUTS. Frequency of micturition was assessed by going through a normal day. We found that the rates of daily micturitions reported during semi-structured interviews and in the questionnaires were exactly the same. Overall, two thirds of the adolescents reported normal voiding habits. The twelve adolescents who reported <4 or >8 daily micturitions got advice how to normalize their voiding frequency. Those who had large residual volumes were advised to “double-void” morning and evening.
4. Discussion

The main finding of this study is that sexual function in adolescent HD males generally is unaffected by minimally invasive ERPT. Furthermore, sporadic LUTS were common, but patient satisfaction with bladder function was very high. This is important information to be passed on to patients and parents.

The finding from this study on HD adolescent males’ ability to get an erection and to ejaculate contribute to the existing, but very limited knowledge on postoperative sexual function in HD males. The ability to get spontaneous erections after both open and minimally invasive ERPT, is reported in nearly 100% of HD males [5-9, 18, 27, 28]. Thus, our results are in line with earlier studies. In contrast to the number of studies examining the ability to get spontaneous erections, very few studies have explored HD males’ ability to ejaculate, and none has reported adolescents’ ability to ejaculate. We found that nearly all adolescents ≥15 years could ejaculate and none reported to have a retrograde ejaculation. A recent study in 16 adult HD males who had undergone ERPT in childhood, found that all could ejaculate and the first ejaculation occurred at median 13 years [9]. Studies from the 1970s including patients operated with the open Swenson procedure report absent ejaculation in a few patients [20, 27]. A recent study found that 2% of 94 adult HD males had retrograde ejaculation after mostly open Duhamel pull-through [10]. Since so few studies have explored ejaculation in HD males, one cannot draw any firm conclusions, but it seems that the ability to ejaculate is preserved in the great majority of HD males.

In a previous qualitative study we reported that adult HD males expressed good sexual self-esteem and few problems with intimate relationships [29]. This is supported by a recent quantitative study reporting that sexual quality of life in adult HD males was comparable to controls [10]. The HD men in our previous study recommended addressing sex from early teens during follow-up and explain to the teenagers how the operation could interfere with later sexual activity. Some had wondered if they should take any precautions concerning sexual activities because of previous surgery. Based on this and the experience from talking about sex with the HD adolescents, we suggest that sex is discussed with HD teens.

LUTS were reported by nearly half of the male HD adolescents, but the majority had only sporadic LUTS. This observation is in accordance with recent studies which report LUTS in
37–68% of HD patients of both genders operated with ERPT [9, 15, 16]. As shown in a large population study, we report urge and stress incontinence in very few adolescent HD males [30]. Overall, we found that one out of ten male HD adolescents had urinary incontinence. This is in line with a systematic review where urinary incontinence was found in up to 11% of patients after open and minimally invasive ERPT [4]. None of the adolescents reported social problems related to urinary incontinence which is in accordance with other studies [9, 15, 16]. We found that none of the adolescents had enuresis. Another study reported increased frequency of enuresis in HD patients compared to the age-matched controls, but the HD patients in that study were young; median 8 years [15]. Recent large studies have found that enuresis are more common in constipated HD children, and that poor bowel function is associated with frequent urinary incontinence regardless of age [15, 31]. It is well known that both hypospadia and neurologic diseases, especially in the central nervous system, could affect patients’ LUTS-profile negatively [32, 33]. One male adolescent had a neurologic disease without intellectual impairment, and was the only one with low satisfaction with own bladder function. It is also important to emphasize that the frequency of LUTS in this and most studies we have compared our results with, report findings in non-syndromic HD patients [9, 15, 34]. In syndromic HD patients, both frequency and severity of LUTS are different from those without a syndrome [35, 36].

Very few papers report results from postoperative urodynamic studies in HD patients, and only one recent study presents findings from urodynamic studies after minimally invasive ERPT [9]. Interestingly, only half of the uroflowmetry curves were normal (bell-shaped) in both studies. In contrast, two large studies of 1268 and 950 healthy children aged 4-14 years report 80-90% normal curves [37, 38]. The HD adolescents’ frequency of staccato and interrupted curves were not different from healthy controls, but plateau curves were more common. Plateau curves are found in 5% of healthy controls, and often when voided volumes are large [39]. The majority of the adolescents in our study had voided volumes exceeding their expected bladder capacity. The most plausible explanation is that they waited too long before they voided as most reported a strong urge to void. If we had done a second urodynamic study, this source of error might have been ruled out.

There is a growing recognition that HD is associated with CAKUT. CAKUT occur in 4-25% of HD patients compared to 0.3-1.7% in the general population [24, 40-45]. Among those who had investigations of the urinary tract, we found that 24% fulfilled the criteria for CAKUT. This percentage is probably not reflecting the true frequency of CAKUT in this
population because there was no systematic screening and several investigations had been done due to urinary symptoms or prenatal findings. Many studies advocate that all HD patients should be screened for CAKUT. Whether this is beneficial is debatable, as few with CAKUT need any treatment [15, 40, 42]. Only 6% of the adolescents in this study had undergone an operation due to CAKUT. This is in line with other studies which find that only a minority of HD patients with CAKUT required medical or surgical treatment [15, 24, 46, 47].

The main strengths of this study are the high rate of attendance and that an independent investigator interviewed the adolescents and their parents and did the chart reviews. The use of a validated questionnaire and urodynamic studies also strengthen the generalizability. The modified version of the DAN-PSS have been extensively used to report LUTS in HD patients and controls, thereby making it easier to compare and contextualize the results from this present study with other studies in HD patients [9, 16, 30, 31, 48]. We did not use a questionnaire to evaluate sexual function. It is possible that the adolescents would have answered more honest if a questionnaire had been used. In addition, some may regard asking 12-14 year old male adolescents about sexual function a limitation. Based on the adolescents’ reporting on sexual function, one could talk about sexual function from the age of 12, but study male patients’ sexual function at a higher age.

To conclude, this study suggests that minimally invasive ERPT preserves sexual function and does not induce lower urinary tract symptoms in adolescent HD males. Furthermore, male HD adolescents appreciate the opportunity to talk about sex, and this should be a part of transitional care.

Supplementary Material

**Appendix 1.** Modified version of the Danish Prostatic Symptom Score (DAN-PSS) on lower urinary tract symptoms.

Conflict of Interest

The authors report no conflict of interest.
Acknowledgments

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Table 1. Demographics of male adolescents with Hirschsprung disease (n=35). One adolescent had more than one associated anomaly.

<table>
<thead>
<tr>
<th>Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (min-max), years</strong></td>
<td>14.9 (12-18.4)</td>
</tr>
<tr>
<td><strong>Length of aganglionosis</strong></td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid colon</td>
<td>33 (94%)</td>
</tr>
<tr>
<td>Proximal to rectosigmoid colon</td>
<td>2 (6%)</td>
</tr>
<tr>
<td><strong>Endorectal pull-through operations</strong></td>
<td></td>
</tr>
<tr>
<td>Total transanal</td>
<td>25 (71%)</td>
</tr>
<tr>
<td>Laparoscopy assisted</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Laparotomy assisted</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Associated anomalies</strong></td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Neurologic(^1)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Urinary tract(^2)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Neoplasm(^3)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

\(^1\)Hydrocephalus and a neurological disease without intellectual impairment.

\(^2\)Kidney hypoplasia, hydronephrosis, and vesicoureteral reflux.

\(^3\)Benign coecal tumor removed prior to diagnosis of Hirschsprung disease.
Table 2. Results of selected items from a questionnaire on lower urinary tract symptoms answered by male adolescents operated for Hirschsprung disease (n=32).

<table>
<thead>
<tr>
<th>Daily micturitions</th>
<th>1-3/day</th>
<th>4-8/day</th>
<th>&gt;8/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (34%)</td>
<td>20 (63%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Micturitions at night</th>
<th>Never</th>
<th>1/night</th>
<th>2/night</th>
<th>≥3/night</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29 (91%)</td>
<td>3 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Never</th>
<th>Seldom</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straining</td>
<td>24 (75%)</td>
<td>7 (22%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Urge</td>
<td>23 (72%)</td>
<td>7 (22%)</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>31 (97%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>29 (91%)</td>
<td>3 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Passive incontinence</td>
<td>31 (97%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Results from urodynamic studies in male adolescents operated for Hirschsprung disease. Results are reported only for adolescents with a voided volume >50% of expected bladder capacity (n=28) and measured residual volume (n=26).

<table>
<thead>
<tr>
<th></th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voiding time (s)</td>
<td>40 (15-72)</td>
</tr>
<tr>
<td>Duration of flow (s)</td>
<td>36 (15-70)</td>
</tr>
<tr>
<td>Time to max flow (s)</td>
<td>12 (2-32)</td>
</tr>
<tr>
<td>Max flow rate (ml/s)</td>
<td>26 (15-42)</td>
</tr>
<tr>
<td>Mean flow rate (ml/s)</td>
<td>16 (7-27)</td>
</tr>
<tr>
<td>Voided volume (ml)</td>
<td>517 (253-1060)</td>
</tr>
<tr>
<td>Residual volume (ml)</td>
<td>21 (0-193)</td>
</tr>
</tbody>
</table>