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Full-thickness rectal biopsy in children suspicious for Hirschsprung's disease is safe and yields a low number of insufficient biopsies

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ABSTRACT

Introduction: The diagnosis of Hirschsprung's disease (HD) relies on the histological demonstration of aganglionosis in the bowel wall. Biopsies may be obtained by rectal suction biopsy (RSB) or by transanal full-thickness excision biopsy (FTB). The objective of the present study was to evaluate the frequency of complications and inconclusive biopsies after FTB in children referred with suspicion of HD. The secondary objective was to calculate the frequency of proven aganglionosis.

Methods: A retrospective chart review was performed of all patients under the age of 16 years who underwent transanal FTB during the time period of 2008–2014.

Results: A total of 555 patients were included in the review. Inconclusive biopsies were found at the primary biopsy in 35 patients (5.9%). Aganglionosis was found in 12% of the cases. The complication rate was 6.6% (39 patients), 85% of which were classified as a Clavien–Dindo I–II and 15% were classified as Clavien–Dindo III.

Conclusions: In this retrospective evaluation of FTB for the diagnosis of HD, the frequency of inconclusive biopsies at primary attempt was low and the complication rate was relatively high. However, most were minor complications.

Level of evidence: III

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The diagnosis of Hirschsprung's disease (HD) relies on histological confirmation of complete absence of ganglion cells in the myenteric and submucosal plexus of the affected segment of the large bowel, together with hypertrophy of nerves. As the rectum always is involved in the disease, transanal biopsy of the distal rectum is considered the gold standard for primary diagnosis.

The biopsies can be obtained either by transanal full-thickness excision biopsy (FTB) or rectal suction biopsy (RSB). In Europe, 39% of surgeons perform FTB [1], but worldwide, over 80% of centers are using RSB for diagnostic workup [2].

In the original paper from 1955 by Swenson et al. [3], only one complication (postoperative bleeding) in 40 patients undergoing FTB was reported. In a recent paper with only 13 patients, no serious complications were reported [4]. In a recent systematic review, the reported complication rate of RSB was 0.65% [5], but when taking all the available literature into account, it varies from 0 to 15% [4,6–8].

The number of inconclusive biopsies at RSB varies in the literature. A recent systematic review showed 10.1% diagnostically insufficient

biopsies at initial biopsy [4]. Regarding FTB, the frequency of diagnostically insufficient biopsies varies between 0 and 13% in relatively small series of 72 included patients at maximum [4,7,9].

The objective of the present study was to evaluate the frequency of inconclusive biopsies and complications after FTB in children referred with suspicion of HD. The secondary objective was to calculate the frequency of proven aganglionosis.

1. Methods

We performed a retrospective chart review of all patients (<16 years) who had a FTB in the period from 2008-01-01 to 2014-12-31 at Odense University Hospital (OUH), Denmark, which is a tertiary referral center for pediatric surgery of western Denmark serving approximately 2.6 million inhabitants. All patients referred with suspicion for HD had an FTB without other preoperative screening modalities or clinical evaluation. FTB was the standard method during the entire study period and was performed under general anesthesia without perioperative prophylactic antibiotics, except for children with an impaired immune system or under immune suppressive treatment.

For FTB, a full-thickness suture was placed in the posterior wall of the rectum, approximately 2–3 cm above the dentate line. The rectal wall was raised by traction on the suture and a 3–5 mm FTB was cut with scissors. Hemostasis was secured by bipolar electrocoagulation, and the defect was sutured. Postoperative complications were defined

Abbreviations: HD, Hirschsprung's Disease; FTB, full thickness excision biopsy; RSB, rectal suction biopsy; CDC, Clavien–Dindo Classification; OUH, Odense University Hospital; REDCap, Research Electronic Data Capture; OPEN, Odense Patient data Explorative Network; FTBs, full-thickness rectal biopsies.

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Table 1

Frequency of negative, confirmative, and inconclusive biopsies at first, second, and third attempt of full-thickness excision biopsy (FTB). HD = Hirschsprung's disease. Mean age is given in months.

	First biopsy (n = 555)	Second biopsy (n = 35)	Third biopsy (n = 3)
Negative for HD (mean age)	464 (37.1)	23 (39.5)	1 (59)
Positive for HD (mean age)	56 (24.3)	9 (27.0)	2 (2)
Inconclusive (mean age)	35 (34.7)	3 (21)	0 (—)

as any contact to the department by either phone or admittance, and classified according to the Clavien–Dindo Classification (CDC).

Inconclusive biopsies were defined as: 1) specimens without identifiable ganglion cells and without the representation of submucosa and/or the interface between the internal and external muscle layers of the muscularis propria, or 2) specimens where the pathologist deemed the biopsy inconclusive owing to poor quality or size. An electronic search was conducted in the Pathology Data Base of the Department of Pathology, Odense University Hospital, which is a subunit of the Danish Pathology Data Base (DPDB). The following diagnostic codes: "T68*" ("rectal mucosa") and "TX9600" ("rectum"), combined with M21000 ("aganglionosis") or M01000 ("normal tissue") or M09011/M09010 ("material not suitable for a conclusive diagnosis") were used. Study data were managed using the REDCap (Research Electronic Data Capture) tools hosted by Odense Patient Data Explorative Network (OPEN).

Stata software version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP®) was used for statistical analysis. Continuous data were calculated as medians and ranges. Categorical data were tested by Pearson's chi-squared test. To compare the frequency of positive biopsies for HD under with above 1 year of age the Fischer's exact test was used.

The study was approved by the Danish Patient Safety Authority, case number 3-3013-1110/1, and the Danish Data Protection Agency, file number 15/19986. No financial funding was received.

2. Results

Initially we retrieved a total of 682 biopsies. We found 38 specimens from resected colonic segments coded as rectal biopsies. Eighteen biopsies from 14 patients (seven with age > 15 years, seven with wrong coding) were erroneously registered and excluded, and thus 626 biopsies were included in the study. Thirty-three patients were biopsied in duplicates, 35 patients had rebiopsy and three patients had two rebiopsies. Thus, in total 593 FTB procedures were performed in 555 patients. For a short time period, it was common at our department to perform FTB in duplicates. All calculations were based on the number of patients, without paying attention to the number of biopsies performed at each procedure. Median age at time of biopsy was 20 months (range 0–191). There were 322 boys (58%) and 233 girls (42%) (Table 1).

In children below one year compared to above one year, 19.2% and 7.3% were positive for HD ($p = 0.001$). Forty percent of all biopsies and 64% of all positive biopsies were taken from patients below one year of age (Table 2). Fig. 1 shows the cumulative number of positive biopsies in relation to age.

Table 2

Negative and positive biopsies in children below and above one year of age.

	Negative biopsy	Positive biopsy	Total
0–1 year	180 (80.72%)	43 (19.28%)	223 (100%)
> 1 year	308 (92.77%)	24 (7.23%)	332 (100%)
Total	488 (87.93%)	67 (12.07%)	555 (100%)

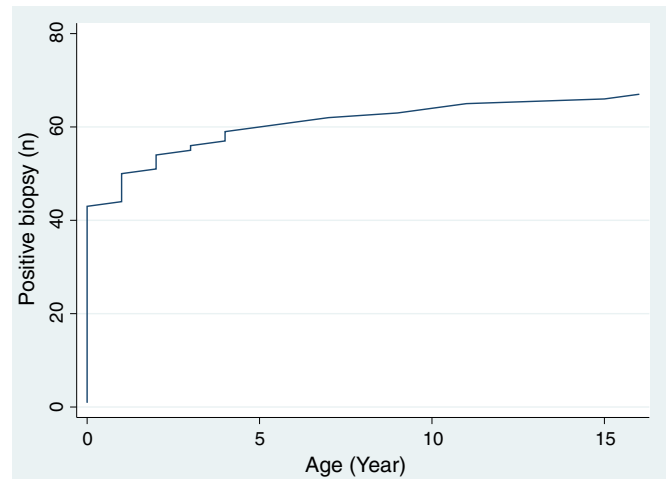


Fig. 1. Cumulative number of positive biopsies in relation to age.

We registered a total of 39 complications (6.6%) and four of these patients had HD (10%). Thirty-three patients experienced complications rated as CDC I–II (Table 3). None of the four patients with bleeding needed transfusion, and seven of the 22 patients with fever received antibiotic treatment.

Six patients experienced complications that were classified as CDC III–B with reoperation or anal examination in GA. In two patients, the sutures were removed but no pathology was found, and the course was otherwise uneventful. Two patients had a rectal abscess that was drained and treated for three days with intravenous antibiotics (Table 3).

Two patients needed a diverting stoma. The first was a two-year-old boy diagnosed with a perirectal abscess two days after FTB. The abscess was primarily drained, but owing to recurrent pain and fever a diverting colostomy was placed. The stoma was reversed one month later followed by an uncomplicated course. The patient was later diagnosed with hereditary sensory and autonomic neuropathy (HSAN) type 3, and is still treated with laxatives for severe constipation five years later. The other patient was a 15-year-old boy with lifelong constipation. He underwent rebiopsy because of an inconclusive biopsy at first attempt. One week after the rebiopsy, he presented with rectal bleeding and severe morphine resistant pain at defecation. Abdominal plain X-ray showed colonic ileus owing to fecal impaction. A diverting colostomy was placed and the rebiopsy was positive for HD.

In 35 patients, the primary biopsy was inconclusive (6.3%), one specimen was lost during shipment from the operation room to the department of pathology, and one was inconclusive for technical reasons in the lab. Hence, there were 33 truly inconclusive, primary biopsies (5.9%) (Table 1). At rebiopsy, we found aganglionosis in 40% of the biopsies, and at second rebiopsy, aganglionosis was found in 66% (Table 1).

Overall, a total of 67 biopsies (12%) were confirmative for HD. No significant difference was found concerning age or rate of complications.

In 32 patients, relative anal stenosis were found and treated by dilation. All were negative for HD.

Table 3

Complications according to Clavien–Dindo Classification (CD), after full-thickness biopsies (FTBs) in 555 patients.

Symptoms	CD-1	CD-2	CD-3b	Treatment
Bleeding	4			None
Fever	15	7		Antibiotics in CD-2
Abscess			2	Surgical drainage
Perforation			1	Laparotomy and stoma
Fecal impaction			1	Stoma
Pain		7		Paracetamol
Other			2	Anal examination in general anesthesia

3. Discussion

Our series includes the largest number of FTBs for the diagnosis of HD published in the literature. We found a low frequency of inconclusive biopsies with an acceptable complication rate.

The rate of inconclusive biopsies represents one of the most important criteria when evaluating the quality of rectal biopsies as a diagnostic tool in HD. In one study, no inconclusive biopsies were found in either the RSB or the FTB group [10]. In another study, 8% of FTBs were inconclusive [9]. In some studies based on RSBs, the rate of inconclusive biopsies was as high as 24%, but in the latest and largest meta-analysis, the rate was 10% [8]. A systematic review reported a mean sensitivity of 98% for RSB [5], which indicates a risk of missed diagnoses of 2%. In our study, the rate of inconclusive biopsies was 5.9%, and none of the patients with a normal biopsy was later diagnosed with HD. Whether this is a significant difference is not possible to evaluate but the clinical consequence of a missed HD diagnosis may be serious.

In the present study, we found a total complication rate after FTB of 6.6%, but only 1% with CDC IIIb. In only two cases, major surgery with placement of a stoma was necessary, and in one patient, this could not be ascribed to the biopsy procedure. The rate of complications after rectal biopsy for HD varies in the literature. In the largest series of FTBs, the complication rate was not reported [10]. The overall complication rate in RSB ranged 0–15% [4–8,11–16]. In all of the referred studies, the type of complications was not described in detail regarding severity or necessity of treatment. In a recent study, the rate of complications was lower when RSB was performed under GA (0% vs. 2%) compared to non-GA biopsies [17]. Fever was the most common complication in our series, as opposed to studies using RSB, where bleeding was the most common complication [2]. Bowel perforation rate of 0.06% at RSB was reported in the review from Friedmacher et al. [2]. Postbiopsy stoma formation was necessary in two of our cases (0.36%), and in one case this was because of HD and not directly related to the FTB procedure. No necessity of stoma placement has been reported after RSB.

The advantage of RSB over FTB is the avoidance of general anesthesia (GA) especially in children below one year. The minor, not patient related disadvantage is a more complex, time-consuming histological preparation and examination of RSB compared to FTB, because the RSB is more superficial, typically only involving the mucosal and submucosal layer [17]. It may be necessary to cut numerous (up to 75 or more) sections from RSBs for conclusive examination in case ganglion cells are not identified after initial step sectioning [4]. Moreover, a higher number of biopsies have to be obtained when RSB is used, ranging 1–5 biopsies per intervention [7,13,18].

FTB yields deeper and larger tissue samples, allowing the evaluation of the submucosal as well as the myenteric plexus, while RSB produces more superficial biopsies without representation of the myenteric plexus [4]. The presence of ganglion cells effectively rules out HD, and if these are identified in the first few step sections, no further sectioning is needed. A further limitation of RSB is that it is not able to detect diseases of the muscularis propria (i.e., myopathies or certain types of ganglionitis). The disadvantage of FTB is the requirement of GA. Recent studies have shown that it seems unlikely that anesthetic drug exposure in young children will influence long-term cognitive outcome [19]. It has also been demonstrated that parents willingly consented on GA when this could facilitate the diagnosis [20].

The surgical procedure of choice at our department is the pull-through technique, and we have not experienced any complications or difficulties that could be related to a previous FTB.

No screening with contrast enema (CE) or anorectal manometry (ARM) was performed after referral owing to the relative poor sensitivity/specificity of 91%/94% and 70%/83%, respectively. Our department serves as a tertiary referral center for rectal biopsy on the suspicion for HD. The children may have undergone other diagnostic procedures previously, but that was not the aim of the present study to investigate. With an HD-positivity of 12%, the number of positive biopsies was

comparable to other series, although it varies from 5% to 42% [6,8,9,16,17,19].

We found only one other disease during FTB (anal stenosis), none of the patients had positive biopsies, and no complications were seen after dilation; the clinical importance of this has not been investigated.

A strength of the present study is its size and that there were no procedural changes during the inclusion period. A limitation of this study is its retrospective nature, and we can therefore not totally exclude that a few minor complications may not have been reported. Reporting of major complications requiring treatment, on the other hand, was complete.

4. Conclusion

We found that FTB performed in patients suspected of HD had a relatively high rate of complications (6.6%), but most complications were of minor severity and only one out of 555 patients had a serious complication directly related to the FTB procedure. Our data show that FTB yields a high rate of conclusive biopsies at primary attempt.

Conflicts of interest

None

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