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Diagnosing Hirschsprung Disease in Children Younger than 6 Months of Age: Insights in Incidence of Complications of Rectal Suction Biopsy and Other Final Diagnoses

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Abstract

Background The gold standard for diagnosing Hirschsprung disease (HD) in patients younger than 6 months is pathological examination of rectal suction biopsy (RSB). The aim of this study was to gain insight into the following: (1) complications following RSB, (2) final diagnosis of patients referred for RSB, and (3) factors associated with HD.

Methods Patients suspected of HD referred for RSB at our center were analyzed retrospectively. Severity of complications of RSB was assessed using Clavien–Dindo (CD) grading. Factors associated with HD were tested using multivariate logistic regression analysis.

Results From 2000 to 2021, 371 patients underwent RSB because of infrequent defecation, at a median age of 44 days. Three patients developed ongoing rectal bleeding (0.8%) graded CD1. Most frequent final diagnoses were: HD (n = 151, 40.7%), functional constipation (n = 113, 31%), idiopathic meconium ileus (n = 11, 3%), and food intolerance (n = 11, 3%). Associated factors for HD were male sex (odds ratio [OR], 3.19; confidence interval [CI], 1.56–6.53), presence of syndrome (OR, 7.18; CI, 1.63–31.69), younger age at time of RSB (OR, 0.98; CI, 0.85–0.98), meconium passage for more than 48 hours (OR, 3.15; CI, 1.51–6.56), distended abdomen (OR, 2.09; CI, 1.07–4.07), bilious vomiting (OR, 6.39; CI, 3.28–12.47), and failure to thrive (OR, 8.46; CI, 2.11–34.02) (model $R^2 = 0.566$).

Keywords
- Hirschsprung disease
- rectal suction biopsy
- complications
- associated factors
- differential diagnosis

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Conclusion RSB is a safe procedure with few and only minor complications. In the majority of patients referred for RSB under the age of 6 months, HD was found followed by a functional cause for the defecation problems. RSB should be obtained on a low threshold in all patients under the age of 6 months with the suspicion of HD.

Introduction

Hirschsprung disease (HD) is a congenital bowel disorder, affecting 1 in 5,000 live births.[1] It is caused by a disrupted migration of neural crest cells during fetal development, resulting in absence of ganglia in the distal bowel, causing fecal stasis.[2] This results in patients presenting with a wide variety of nonspecific symptoms for HD, such as problems passing feces (delayed meconium passage), distended abdomen, and bilious vomiting.[3–5] These symptoms are also part of diagnoses such as functional constipation, meconium ileus, intestinal dysmotility syndromes, and cystic fibrosis.[4–7]

In case of clinical suspicion of HD in patients below 6 months of age, pathological examination of a rectal suction biopsy (RSB) is performed, which is the gold standard for diagnosing HD.[8,9] In older patients, full-thickness biopsies (FTBs) are more prevalent because larger amounts of tissue may be necessary and anesthesia can be required.[10,11]

It is important to prevent any delay in diagnosing HD in order to start adequate treatment and prevent severe fecal stasis, as well as further bowel dilatation and Hirschsprung-associated enterocolitis.[12,13] Also, inadequate bowel decompression can lead to possibly life-threatening complications, underlining the importance of early recognition of HD.[14] However, recognition based on clinical findings remains troublesome. As a consequence, the threshold to take RSB in patients with potential HD is low. Indeed, it has been shown that only one out of five patients undergoing RSB is diagnosed with HD.[15] The advantage of maintaining a low threshold to obtain RSB in patients suspected of HD is that the diagnosis of HD is rarely missed. However, the disadvantage of this approach is that a large group of patients unnecessarily faces invasive examination with a potential risk of complications.[16] RSB has a low complications rate (0.65%), but data are lacking describing the severity of complications following RSB.[15]

Therefore, we studied patients suspected of HD undergoing RSB, below 6 months of age, aiming to give insight into the following: (1) the incidence and severity of complications caused by RSB, (2) the final diagnoses of patients referred for RSB, and (3) factors associated with HD.

Methods

Patient Population

All eligible patients from two university hospitals of the Amsterdam university medical centers (Academic Medical Center and VU Medical Center) presenting between 2000 and 2021 were retrospectively selected via the Dutch Nationwide Pathology Databank PALGA. The following search terms were used: ganglion, HD, and biopsy. Exclusion criteria were patients older than 6 months at the time of RSB, patients/caretakers who gave no informed consent, and patients for whom details about the RSB were missing.

Clinical Procedure

In case of suspicion of HD based on clinical symptoms, such as failure to pass meconium ($>$ 48 hours), bilious vomiting, distended abdomen, or unexplained constipation, an abdominal X-ray was performed. The abdominal X-ray was examined by a radiologist experienced in pediatric gastroenterology and found suggestive for HD when signs of distal bowel obstruction were present, including multiple dilated bowel loops in combination with absent rectal gas.[17] In patients with clinically or radiologically suspected HD, RSB was obtained on a low threshold.[18] RSBs were taken without sedation by experienced pediatric surgeons. For the RSB, the Rbi2 Suction Rectal Biopsy System instrument (Aus Systems, Charles Sturt, Australia)[19] was used to obtain one to five small samples of mucosa and submucosa at 2 cm ventrally and 2 and 4 cm dorsally from the anal verge for pathological examination. RSBs were stained using acetylcholinesterase (AChE) on frozen sections until the end of 2011 and calretinin staining on paraffin sections from 2012 onward, both of which were combined with slides stained with hematoxylin and eosin (H&E).[20,21] Anorectal manometry was not used in the diagnostic work-up because RSB is the gold standard to diagnose HD.[22] Contrast enema was performed in cases with confirmed HD to estimate the length of disease.[9]

Examination of the Slides

Gastrointestinal pathologists with ample experience in pediatric gastroenterology analyzed the biopsies. Slides were deemed positive for HD in case of absent ganglia on H&E staining, combined with increased AChE reactivity of nerve fibers in muscularis mucosae and mucosa, with or without hypertrophic submucosal nerve fibers (diameter exceeding 40 µm). Slides were deemed negative for HD when ganglia were present. With respect to the calretinin staining, cases were deemed positive for HD when slides showed calretinin negativity of nerve fibers in mucosa, muscularis mucosae, and submucosa, in addition to absence of ganglia.[21] If slides were not conclusive, RSB were repeated or FTBs were performed. Slides were considered inconclusive if the quality of the slides was too low for detection of ganglia or thickened nerve trunks or if the particular slide did not include the muscularis mucosae and submucosa. However, diagnostics

were not repeated if patients recovered spontaneously and there was therefore no longer a suspicion of HD.

Data Extraction

Medical records of all eligible patients were extracted by multiple authors (L. B., H. L., and M. M.) and stored in a Castor Electronic Data Capture database. Data validation was done by checking 10% of the recorded data by other researchers. If there were inconsistencies in over 1% of the patient records, the entire record was checked. The following patient details were extracted: sex (male/female), comorbidity (yes/no), syndrome (yes/no), familial HD (yes/no), prematurity ($<$ 37 weeks, yes/no), dysmaturity (defined as low birth weight in relation to the gestational age, yes/no), time to meconium passage following birth ($<$ 24 hours, 24–48 hours, $>$ 48 hours), symptoms at presentation (distended abdomen, bilious vomiting, blood in feces, ileus, hard stools, diarrhea; yes/no), number of samples per RSB, inadequate RSB (yes/no), staining RSB (AChE, calretinin), complications due to RSB (yes/no), type of complications (persistent rectal bleeding, perforation, sepsis), and final diagnosis (HD/other). In the case that the final diagnosis was lacking in the medical record, we contacted the patient's general practitioner to obtain information about the final diagnosis.

Measurements and Definition

We retrospectively assessed the overall prevalence of complications in all patients as the proportion of patients in our cohort that had a history of at least one complication according to the Clavien–Dindo (CD) classification of surgical complications[23] within 30 days after RSB. CD grade 1 and 2 were considered minor complications and CD 3, 4, and 5 were considered major complications.[23] Despite only being validated for scoring postoperative complications in adults, the CD classification met all of the requirements for use as a tool to rate preoperative complications in the current study population. We did not distinguish between grades 3a and 3b because these are clinically irrelevant in pediatric surgery.[24] In case a complication occurred following RSB, the patient's age at the time of RSB, the type of complication (persistent rectal bleeding, perforation, sepsis), and the severity of the complication were recorded. Rectal bleeding was defined as ongoing bleeding including clots for over 2 hours after obtaining RSB. Sepsis was diagnosed using the systemic inflammatory response syndrome criteria for pediatrics.[25]

Final diagnosis following RSB was reported by calculating the prevalence of each final diagnosis. Functional constipation was diagnosed using the Rome IV criteria for infants and toddlers.[26,27] We used the characteristics of Waldhausen and Richards to define idiopathic meconium ileus: inspissated meconium impacted in the distal ileum leading to abdominal distention, bilious vomiting, and failure to pass meconium within 48 hours and radiography showing multiple loops of bowel of various sizes with ground-glass appearance without the presence of air–fluid levels with no identifiable cause.[28] Gastroenteritis was diagnosed when the following symptoms were present: clinical signs of bowel inflammation without previous bowel obstruction and not requiring intravenous antibiotics.[29] The presence of necrotizing enterocolitis was defined using Bell's criteria stage IIA or higher: presence of apnea, bradycardia, lethargy and temperature instability with gastrointestinal moderate abdominal distension, hematochezia, absent bowel sounds and the radiological finding of an ileus with dilated bowel loops, and focal pneumatosis.[30]

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, United States). Identification of factors associated with HD was done by multivariate logistic regression analysis. Forward Wald selection was used to select variables significantly related to the presence of HD and assessment of confounding (increase in B-coefficient of $>$ 10%) and effect modification (significant interaction term). We report the percentage of variance explained by the final model in terms of adjusted R^2. For variables significantly associated with the presence of HD, we report the odds ratio (OR) and the accompanying 95% confidence interval (CI).

Ethics

The Institutional Review Board approved this study (W18_160#18.198). All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments. Caretakers of all included patients provided informed consent to participate in this study.

Results

Population Characteristics

We analyzed 693 patients, of whom 322 were excluded: in 138 patients, the RSB was performed elsewhere; 139 patients were older than 6 months of age at RSB; in 3 patients, the RSB was performed before the year 2000; in 26 patients, data about the RSB were missing; and 16 caretakers did not provide informed consent to participate in this study. Consequently, 371 patients were included in this study, of whom 151 patients (40.7%) were diagnosed with HD. Of all the included patients, 240 (64.7%) were male, with a mean gestational age of 37.3 weeks (standard deviation 3.5 weeks). Twenty-eight patients suffered from a syndrome (7.5%), including 19 patients with Down's syndrome (5.1%), 74 patients (19.9%) were born premature, and 39 patients (10.5%) were born dysmature. Abdominal X-ray was performed in 176 patients with RSB (47.4%), showing fecal impaction in 34 patients (9.2%), rectal gas in 108 patients (29.1%), ileus in 17 patients (4.6%), and abdominal distention in 118 patients (31.8%). Baseline characteristics stratified for having HD are described in ►Table 1.

Rectal Suction Biopsy

The median age at the time of RSB was 44 days (range, 2–175) with a median number of three samples taken per session (range, 1–5), resulting in a total of 1,260 samples. In 62 patients (16.7%), the examination of the first RSBs was inconclusive and as a consequence in 42 of them (11.3%)

Table 1 Characteristics of all included patients ($n = 371$)

	HD ($n = 151$)	No HD ($n = 220$)
Patient characteristics		
Male sex, *n* (%)	114 (75)	126 (57)
Comorbidity present, *n* (%)	43 (28)	42 (19)
Missing, *n* (%)	1 (1)	11 (5)
Syndrome, *n* (%)	20 (13)	8 (3.6)
Down's syndrome, *n* (%)	16 (10.5)	3 (1.4)
Pierre Robin sequence, *n* (%)	0 (0)	2 (0.9)
Other,[a] *n* (%)	4 (2.6)	3 (1.4)
Missing, *n* (%)	0 (0)	0 (0)
Familial HD, *n* (%)	12 (8)	7 (3)
Prematurity, *n* (%)[b]	25 (16)	49 (22)
Missing, *n* (%)	7 (5)	43 (20)
Dysmaturity, *n* (%)[c]	11 (7)	28 (12)
Missing, *n* (%)	12 (8)	50 (23)
Clinical characteristics		
Meconium passage > 48 h, *n* (%)	82 (54)	44 (20)
Missing, *n* (%)	9 (6)	38 (17)
Age at time of RSB (d), mean (SD)	22 (30)	60 (45)
Missing, *n* (%)	0 (0)	0 (0)
Symptoms present		
Distended abdomen, *n* (%)	100 (66)	80 (36)
Bilious vomiting, *n* (%)	100 (66)	53 (24)
Blood in feces, *n* (%)	1 (1)	4 (2)
Ileus, *n* (%)	15 (10)	8 (4)
Hard stools, *n* (%)	0 (0)	25 (11)
Diarrhea, *n* (%)	0 (0)	4 (2)
Failure to thrive, *n* (%)	19 (13)	11 (5)
Abdominal X-ray, *n* (%)	67 (44.3)	101 (45.9)
Distended bowel, *n* (%)	65 (97.0)	53 (52.3)
Rectal gas, *n* (%)	23 (34.3)	85 (84.2)
Fecal impaction, *n* (%)	17 (25.4)	17 (16.8)
Ileus, *n* (%)	9 (13.4)	8 (7.9)

Abbreviations: HD, Hirschsprung disease; RSB, rectal suction biopsy; SD, standard deviation.

[a]Other syndromes from patients with HD included: Multiple endocrine neoplasia type 2A, Mowat–Wilson, DiGeorge, and cat eye syndrome. Other syndromes from patients without HD included: Silver–Russel syndrome, Chung–Jansen syndrome, and partial trisomy of 3q26.3-pter.

[b]Prematurity: < 37 weeks.

[c]Dysmaturity: low birth weight in relation to the gestational age.

a second RSB was taken, of which 13 RSBs (3.5%) were inadequate, leading to a third RSB in 1 patient (0.3%) and an FTB in 9 patients (2.4%).

Three patients (0.8%) developed one complication following RSB, all graded CD1. All three patients had ongoing rectal bleeding as complication; one initially had a hemoglobin level of 6.2 mmol/L. The bleeding stopped after 5 hours, resulting in a hemoglobin level of 4.8 mmol/L.

The other two patients had ongoing rectal bleeding for 3 hours. No initial hemoglobin levels were known for these patients. At follow-up, one had a hemoglobin level of 4.8 mmol/L and the other patient had a level of 6.9 mmol/L. All three patients were respiratory and hemodynamically stable, did not require any intervention, and did not develop any other complications.

Final Diagnosis

►Table 2 shows the final diagnoses of all patients in whom RSB was performed, stratified by age.

The most frequently assigned final diagnoses following HD in children with RSB taken at 0 to 3 months of age were as follows: (1) functional constipation ($n = 85$, 27.7%); (2) meconium ileus ($n = 13$, 3.0%); and (3) food intolerances ($n = 7$, 2.3%). For children with RSB taken at 3 to 6 months of age, the most frequently assigned final diagnoses were as follows: (1) functional constipation ($n = 29$, 44.6%); (2) necrotizing enterocolitis ($n = 4$, 6.2%); and (3) food intolerance ($n = 4$, 6.2%).

Factors Associated with HD

Logistic regression analysis with forward selection using the Wald statistics was used to determine factors associated with HD. The final model explained 56.6% (adjusted R) of the variance with the following variables being significantly associated with the presence of HD: male sex (OR, 3.19; CI, 1.56–6.53), presence of a syndrome (OR, 7.18; CI, 1.63–31.69), younger age at time of RSB (OR, 0.98; CI, 0.98–0.85), meconium passage for over 48 hours (OR, 3.15; CI, 1.51–6.56), distended abdomen (OR, 2.09; CI, 1.07–4.07), bilious vomiting (OR, 6.39; CI, 3.28–12.47), and failure to thrive as presenting symptom (OR, 8.46; CI, 2.11–34.02) (►Table 3).

Discussion

This study shows a complication rate lower than 1% in the patients in whom an RSB was taken, with all these complications resolving spontaneously. In patients younger than 6 months of age referred for RSB, HD was the most frequently assigned diagnosis, followed by diagnoses involving functional causes for the defecation problems. Male sex, presence of a syndrome, meconium passage for over 48 hours, distended abdomen, bilious vomiting, and failure to thrive were found suggestive symptoms for the diagnosis HD. In these children, RSB should be obtained as soon as possible, once they are in good clinical and nutritional condition.

The first aim of our study was to identify the prevalence and severity of complications following RSB. In accordance with two systematic reviews,[15,16] we found a low prevalence of complications following RSB. However, our findings contrast with those of a systematic review by Friedmacher and Puri, which included a total of 14,053 RSBs, in 58 cohorts, obtained at a median age of 14.4 months.[15] The systematic review reported more severe complications compared with

Table 2 Final diagnoses stratified by age at the time of RSB

	Total ($n = 371$)	0–3 mo ($n = 306$)	3–6 mo ($n = 65$)
Hirschsprung disease, *n* (%)	151 (40.7)	143 (46.7)	8 (12.3)
Functional constipation, *n* (%)	114 (30.7)	85 (27.7)	29 (44.6)
Idiopathic meconium ileus, *n* (%)	11 (3.0)	11 (3.6)	0 (0)
Ileus, *n* (%)	6 (1.6)	3 (1.0)	3 (4.6)
Food intolerance, *n* (%)	11 (3.0)	7 (2.3)	4 (6.2)
Intestinal malformation, *n* (%)	9 (2.4)	6 (2.0)	3 (4.6)
Necrotizing enterocolitis, *n* (%)	9 (2.4)	5 (1.6)	4 (6.2)
Malrotation, *n* (%)	3 (0.8)	3 (1.0)	0 (0.0)
Cystic fibrosis, *n* (%)	1 (0.3)	1 (0.3)	0 (0.0)
Neurological disorder, *n* (%)	3 (0.8)	2 (0.7)	1 (1.5)
Intestinal pseudo-obstruction, *n* (%)	2 (0.5)	2 (0.7)	0 (0.0)
Anorectal malformation, *n* (%)	2 (0.5)	1 (0.3)	1 (1.5)
Anal achalasia, *n* (%)	6 (1.6)	4 (1.3)	2 (3.0)
Strangulated inguinal hernia, *n* (%)	3 (0.8)	2 (0.7)	1 (1.5)
Unknown, *n* (%)	23 (6.1)	23 (7.5)	0 (0)
Other, *n* (%)[a]	17 (4.6)	8 (2.6)	9 (13.8)

[a]Other diagnoses included: small for gestational age ($n = 1$), neuronal dysplasia ($n = 2$), gastroesophageal reflux ($n = 1$), parasitic infection ($n = 2$), Chung–Jansen syndrome ($n = 1$), perforation unknown cause ($n = 1$), Pierre Robin syndrome ($n = 1$), gastroenteritis ($n = 2$), gastric varices and biliary cirrhosis ($n = 1$), morphine-induced constipation ($n = 1$), cholecystolithiasis ($n = 1$), Silver–Russel syndrome ($n = 1$), aerophagia ($n = 1$), and wish for RSB due to familial HD (n = 1).

Table 3 Multivariate analyses testing factors associated with HD

	OR	95% CI	*p*-Value
Male sex	3.19	1.56–6.53	0.002
Comorbidity present	–	–	–
Syndrome present	7.18	1.63–31.69	0.009
Prematurity	–	–	–
Dysmaturity	–	–	–
Clinical characteristics			
Meconium passage			
< 24 h	–	–	–
24–48 h	1.04	0.41–2.61	0.940
> 48 h	3.15	1.51–6.56	0.002
Age at time of RSB	0.98	0.85–0.98	< 0.001
Symptoms			
Distended abdomen	2.09	1.07–4.07	0.031
Bilious vomiting	6.39	3.28–12.47	< 0.001
Blood in feces	–	–	–
Ileus	–	–	–
Fecaloma	–	–	–
Hard stools	–	–	–
Diarrhea	–	–	–
Failure to thrive	8.46	2.11–34.02	0.003
R^2 Nagelkerke	0.566		

Abbreviations: CI, confidence interval; OR, odds ratio; RSB, rectal suction biopsy.

our study, including rectal bleeding requiring blood transfusion (0.5%), bowel perforation with unknown interventions (0.06%), and sepsis with unknown interventions (0.06%).[15] It is unclear why Friedmacher and Puri reported only major complications in their review. One possibility is that different biopsy suction instruments were used in the studies covered in the review compared with our study.[15,16] However, the types of instruments have not been reported by Friedmacher and Puri and therefore this comparison cannot be made.[15] Based on our data, we suggest a low threshold for obtaining RSBs in young children presenting with symptoms suggestive of HD. Such a low threshold approach is expected to prevent complications caused by delayed or inadequate treatment and the need to use FTB to confirm a diagnosis of HD at an older age, which requires general anesthesia and is associated with a higher complication rate compared with RSB.[14,31]

The second aim of our study was to investigate the final diagnosis of patients referred for RSB. After HD, the most frequent final diagnosis assigned was functional constipation. In accordance with the literature, cystic fibrosis, intestinal malformation, congenital strictures, maternal intoxications, congenital hypothyroidism, and enteric nervous system anomalies were found to be rare organic causes for the observed defecation problems that led to referral of children for RSB in our sample of young children.[7,32,33]

The third aim of our study was to explore factors associated with HD. Knowledge on risk factors associated with HD may enable preselection of patients in need of RSB. We found that male sex, presence of a syndrome, lower age, and symptoms upon clinical presentation including more than 48 hours delay in meconium passage, abdominal distention, bilious vomiting, and failure to thrive were all associated with higher risk for HD. The regression model with these variables explain a total of 56% of the variance in the final diagnostic status assigned (HD yes/no). However, the current model cannot replace a diagnostic tool because a validated predictive model is required.

The finding that HD is more often present in males is in line with the current literature.[34–36] In addition, we found that patients with a syndrome, mainly Down's syndrome, have a higher probability of HD. Indeed, an associated chromosomal abnormality has been reported in 12% of patients with HD.[32] However, some of the HD-associated syndromes are also linked to functional constipation and/or mental retardation, complicating the already difficult (differential) diagnosis of HD.[37] Furthermore, we found that younger age at the time of RSB is associated with higher odds of the diagnosis HD. This was also found in other studies showing that most patients present during the neonatal period around the age of 3 to 4 weeks.[14,38,39]

Our results also show that a patient with meconium passage for over 48 hours following birth, a distended abdomen, and bilious vomiting has significantly increased odds of the diagnosis HD. This is in line with earlier findings showing delayed passage of meconium, abdominal distention, and vomiting to differentiate between patients with HD and patients with idiopathic constipation.[40]

Limitations

There are some limitations to our study, which mainly related to the retrospective study design of the current study. Due to this, we need to take into account that minor complications following RSB may not have been reported in the medical files. Missing data or limited data were the result of the reliance on historical data and due to the transition of paper files to digital files. However, we did exclude patients with incomplete RSB pathological reports and incomplete documentation about symptoms at the time of presentation, thereby limiting the possible impact of incomplete data. Fortunately, the amount of missing data was limited with only data on dysmaturity and the time of meconium passage missing in more than 10% of the patients. We could not test the outcomes of the abdominal X-ray as an associated factor, because this was not applied in all patients. Furthermore, our study carries the risk of selection bias because our center is a national referral center for constipation, which may have led to a selected patient population.

Future Perspective

Our findings suggest that factors increasing the likelihood of a diagnosis of HD in children under 6 months of age are male sex, lower age at RSB, presence of a syndrome, and the following symptoms upon presentation: meconium passage for over 48 hours, abdominal distention, and bilious vomiting. Future studies should focus on the development of a predictive model to determine an individual's probability of having HD, to enable implementation of these associated factors in the clinical setting. A predictive model can potentially accelerate diagnosing patients with HD, resulting in early start of adequate treatment and subsequent reduction of preoperative complications. Furthermore, future work should focus on the possible impact of the use of different instruments to obtain RSBs, as different instruments may potentially result in different complications.

Conclusion

In conclusion, we found that RSB can be considered a safe procedure with a low complication rate with only minor complications without the need for interventions. Therefore, RSB can be obtained on a low threshold in all patients under the age of 6 months presenting with symptoms as meconium passage for over 48 hours, distended abdomen, bilious vomiting, and failure to thrive and thus suspected of HD.

Conflict of Interest
None declared.

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