Growth and Developmental Outcomes of Infants with Hirschsprung Disease Presenting in the Neonatal Period: A Retrospective Study

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Objectives To describe the presentation and progress over the first year of life of neonates with Hirschsprung disease, to describe their physical and developmental outcomes at 12 months of age, and to compare the outcomes of infants with short- vs long-segment Hirschsprung disease.

Study design A retrospective study of neonates born with Hirschsprung disease in Western Australia between January 1, 2001, and December 31, 2010, to review their presentation, progress, growth, and development at 12 months of age.

Results Fifty-four infants were identified (40 with short and 11 with long segment and 3 with total colonic aganglionosis); 9 infants had a recognized syndrome and 1 infant died, unrelated to Hirschsprung disease. A primary pull-through procedure was performed in 97% and 21% of neonates with short- and non–short-segment Hirschsprung disease, respectively; 17 (31%) infants developed anal stenosis requiring dilatations. Enterocolitis occurred in 14 (26%) infants. Griffiths Mental Development Scale scores (1 year) were available in 31 of 45 nonsyndromic survivors: mean general quotient (94.2, SD 8.89) was significantly less than the population mean (P = .007), but the number of infants with developmental delay was within the expected range. Physical growth, except length, appeared adequate in nonsyndromic infants. There were no significant differences in the outcomes of infants with short- vs non–short-segment Hirschsprung disease.

Conclusions At 1 year of age, many infants with Hirschsprung disease have ongoing gastrointestinal problems. Their overall growth appears satisfactory, and most infants are developing normally; however, their mean general quotient appears shifted to the left. Longer-term studies will better define developmental outcomes. *(J Pediatr 2014;165:73-7)*.

Evidence that genetic factors contribute to Hirschsprung disease derives from the observation of an increased risk to siblings (2%-49%) compared with the population incidence.[1,2] Also, there is a dominant pattern of inheritance in several pedigrees of Hirschsprung disease and the frequent association with chromosomal abnormalities, such as Down syndrome, and other syndromes, such as Waardenburg syndrome.[2-4]

Studies have assessed the long-term clinical outcome and bowel function of patients with Hirschsprung disease,[5-8] but there is limited information available on developmental outcomes.[9] Hirschsprung disease is frequently associated with central nervous system anomalies, and there is evidence that similar neural growth factors govern both brain and enteric nervous system development.[10] This may put infants with Hirschsprung disease at higher risk of adverse developmental outcomes. Surgery and general anesthesia in the neonatal period may also contribute to adverse neurodevelopmental outcomes.[11-13]

Tsuij et al[14] found that 25% of 5-year-olds with Hirschsprung disease were at <2nd percentile for weight. Suboptimal growth has also been linked to poor development.[15]

Therefore, our study aims were to describe the clinical characteristics and 12-month progress of a regional cohort (Western Australia) of neonates presenting with Hirschsprung disease, to describe their physical growth and developmental outcomes at 12 months of age, and to compare the outcomes of infants with short- vs long-segment disease.

Methods

This was a retrospective audit of all infants born in Western Australia who were diagnosed with Hirschsprung disease in the neonatal period from January 1, 2001, to December 31, 2010. Princess Margaret Hospital for Children (PMH) is the only institution in Western Australia capable of diagnosing and managing neonatal Hirschsprung disease. Therefore, interrogation of the PMH histopathology and neonatal databases identified all neonatal cases of Hirschsprung disease. Relevant clinical details during the initial hospital stay

ASQ	Ages and Stages Questionnaire
GQ	General quotient
HAEC	Hirschsprung-associated enterocolitis
PMH	Princess Margaret Hospital for Children

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and until 1 year of age were obtained by reviewing the medical records of the cases.

Hirschsprung disease was classified as: (1) short segment if the aganglionic region was limited to the rectum and sigmoid colon; (2) long segment if it extended proximal to the sigmoid colon but not the entire colon; and (3) total colonic aganglionosis if the entire colon was involved but not >50 cm proximal to the ileocecal valve.[16-19] The preferred primary procedure throughout the study period was a laparoscopic assisted endorectal pull through. The Duhamel operation was used in 4 infants with long-segment Hirschsprung disease, after an initial ostomy, at several months of age.

All neonates in Western Australia who undergo major surgery are routinely enrolled in a formal developmental follow-up program and are seen at 4, 8, and 12 months' corrected age. At the 12-month corrected gestational age visit, development is formally assessed using the Griffiths Mental Development Scales.[20-23] Where a Griffiths assessment was not available, 2 other sources of developmental outcomes were used: the Ages and Stages Questionnaire (ASQ)[24] or informal developmental information obtained from the infant's local pediatrician.

The Griffiths Mental Development Scales assess development in 5 separate areas: locomotor, personal and social, hearing and speech, eye and hand coordination, and performance. The 5 subscales are assessed and scored separately and then combined to provide an overall general quotient (GQ) reflecting the child's developmental performance level relative to the general population.[25] All 5 subscales are combined to form a total scale, which has a mean score of 100.2 and an SD of 12.8.[26,27] The majority of Griffiths assessments were conducted by a single developmental pediatrician (J.M.).

The ASQ is a parent-completed screening tool that uses parent observation to assess child development and behavior. The ASQ questionnaire at each age point contains 6 questions in each of 5 domains of development—communication, fine motor, gross motor, problem solving, and personal social—for a total of 30 questions. Answer options for each question include "yes," "sometimes," and "not yet." A "yes" response receives 10 points, "sometimes" receives 5 points, and "not yet" receives 0 points. Each of the 5 domains is scored separately. A score of ≥2 SDs below the mean in any 1 of the domains is considered a "fail" on the ASQ.[24] It is a validated screening tool for identifying neurosensory disability.[28-30]

For our study, the main outcome of interest was suboptimal long-term developmental outcome, defined as a GQ >2 SDs below the mean (ie, GQ <75) or cerebral palsy, blindness (visual acuity of <6/60 in the better eye), or sensorineural deafness requiring hearing aids.

Other outcomes of interest were mild developmental delay defined as GQ between 1 and 2 SDs below the mean (76-88) or mild delay as assessed by the infant's local pediatrician, physical growth at 1 year of age, the incidence of rectal/anal strictures, or stenosis and Hirschsprung-associated enterocolitis (HAEC).

Because chromosomal syndromes and septo-optic dysplasia with panhypopituitarism can affect physical growth and neurodevelopmental outcomes, such patients were excluded from these 2 analyses. However, their data relating to gastrointestinal outcomes were included in the analysis.

The conduct of this study was approved by the PMH Institutional Audit Committee. Parental consent was deemed not necessary, considering the retrospective chart review nature of the study.

Statistical Analyses

Statistical analyses were performed using Stata 12.0 (StataCorp LP, College Station, Texas). Mean and SD values were calculated for normally distributed data. The mean GQ of this study sample was compared with the published healthy population mean using the *t* test, and the magnitude of this difference was evaluated using Cohen *d*, where *d* is the difference between the study and population means divided by the population SD. A *d* of .2 is considered a small effect; .5, a medium effect; and .8, a large effect size.[9,31] The published SD for the normal population was used in calculating this effect size because this would reflect the extent to which our sample compared with the variation found in the normal population. Median, IQR, and range values were calculated for continuous data with non-normal distribution. Wilcoxon matched-pairs sign rank test was used to compare the percentiles at birth with percentiles at 1 year of age. Mann–Whitney 2-sample rank sum test was used to explore the differences between short-segment and long-segment Hirschsprung disease groups for nonparametric data; for comparison of categorical variables between the 2 groups, Fisher exact test was used. For all results, a value of $P < .05$ was considered statistically significant.

Results

We identified 54 cases of Hirschsprung disease during the 10-year study period. **Figure 1** (available at www.jpeds.com) provides a flow diagram of the patients' outcomes over the first year of life. There were 21 (39%) female and 33 (61%) male patients (**Table I**). There were 9 (17%) infants with syndromes: 7 with chromosomal anomalies (Down syndrome, 6; isodicentric chromosome 15, 1), 1 with panhypopituitarism and septo-optic dysplasia, and 1 with cerebral dysgenesis with severe hydrocephalus, who did not survive (his death was not related to Hirschsprung disease). Family history of Hirschsprung disease was present in 2 (4%) infants. All infants had >1 of the following presenting symptoms: abdominal distention (70%); vomiting (61%), most of which was bilious vomits or aspirates; delayed passage of meconium (56%); and a sepsis-like illness such as lethargy and poor feeding (20%).

The majority had short-segment disease (40, 74%); 11 (20%) had long-segment disease, and 3 (6%) had total aganglionosis of the colon with the transition zone in the terminal ileum. For this audit, all infants with non–short-segment disease were classified as having long-segment disease. A