THE YEAR 1987 marked the passage of the first century since the Danish physician Harold Hirschsprung first described two cases of infantile constipation with colonic dilation.\(^1\) The absence of intramural ganglion cells in the colon of these patients was first noted by Tittel\(^1\) and Dalla Valle\(^1\) at the beginning of the 20th century. Although this has since proven to be the pathological definition of Hirschsprung’s disease, a causal relationship between defect and disease was not established until the late 1940s.\(^4,5\)

In 1950, Swenson and Bill shifted attention away from the hypertrophic and dilated proximal segment and described a surgical technique directed at resection of the neurologically deprived distal segment.\(^7\) Subsequent modifications and new interventions were described by Duhamel\(^1\) and Soup\oe.\(^9\)

Over the last 30 years, many studies have examined the clinical presentation, radiological and histological diagnosis, surgical correction, epidemiology and genetic implications of this neurological malformation. Many of these surveys have been limited by the small size of the populations studied. We recently examined the files of all patients with the diagnosis of Hirschsprung’s disease who presented to The Children’s Hospital Medical Center of Boston within the 25-year period beginning in 1961 and ending in the first quarter of 1986. The purpose of the study was to characterize the demographics of the affected population.

Many previous demographic studies have been limited by the small size of their study populations. Such studies have suggested a possible relationship of the occurrence of Hirschsprung’s disease to an increase in maternal age.\(^10\) Some studies have found an association of Hirschsprung’s disease with malformations or disorders of the cellular descendants of the neural crest.\(^11-14\) The purpose of this study was to examine a large population of affected individuals in order to characterize their demography and associated abnormalities. This task was undertaken to gain insight into possible pathogenic mechanisms in Hirschsprung’s disease.

MATERIALS AND METHODS

We collected the 321 files in which Hirschsprung’s disease was listed as a possible diagnosis. Of these, 179 met the criteria for Hirschsprung’s disease: (1) clinical, radiological, or manometric presentation consistent with congenital megacolon; and (2) pathologist’s report clearly demonstrating absence of intramural ganglion cells in either biopsy or surgical colonic specimens. Nearly all cases rejected from the study failed to meet this second criterion.

The data abstracted from the charts included: (1) medical record number; (2) date of birth; (3) sex; (4) race; (5) birth weight; (6) gestational age; (7) maternal age at birth; (8) birth order; (9) type of Hirschsprung’s disease; (10) manner of delivery; (11) presence of family history of Hirschsprung’s disease; and (12) clinical presentation. Not all of these parameters were available in each chart.

Under the general classification of Hirschsprung’s disease, past studies have defined various subclassifications.\(^15-18\) In the present study it was not possible to use these systems because surgical and pathological records often did not describe an exact transition point, but rather the presence or absence of ganglion cells at both margins of resected specimens. Therefore, we found it most useful to differentiate between “long”- and “short”-segment disease. Short-segment disease denoted aganglionosis distal to the splenic flexure; long-segment disease denoted aganglionosis proximal to the splenic flexure. Long-segment disease was itself further subdivided to include total colonic aganglionosis (Zuelzer-Wilson disease).

The data for number of births and births by maternal age and race in the state of Massachusetts represent the analysis of 1961 through 1985 statistics (noninclusive of 1964 and 1965). The
statistics from Massachusetts for the total number of first-borns and first-borns by maternal age and race represent the analysis of all years available, 1969 to 1985.  

RESULTS

Long-Versus Short-Segment Disease

Of the 179 cases in this study, 20 (11%) represent long-segment disease (Table 1). Of these patients with long-segment disease, total colonic aganglionic was present in 13 of 20. Thus, total colonic aganglionosis (Zuelzer-Wilson’s disease) represented 7.3% of the study population as a whole.

Sex

In this sample, 138 patients (77%) were male and 41 (23%) were female, yielding an overall sex ratio of 3.4:1. Short-segment disease had 128 males (80%) and 31 females (20%) for a sex ratio of 4:1. Of the 20 patients with long-segment Hirschsprung’s disease, 10 (50%) were male and 10 (50%) were female, for a sex ratio of 1:1 (Table 1). Of the 13 patients with Zuelzer-Wilson’s disease, 8 were female and 5 were male for a female to male ratio of 1.6:1.

Race

Of the 179 children, 161 were white and 18 were nonwhite (9 black, 8 Hispanic, and 1 oriental) (Table 1). These figures likely reflect the race distribution of the referral base of this hospital. No race-specific analysis was performed.

Birth Weight and Gestational Age

Birth weight and gestational age were both available in 127 cases. One of these parameters was available in an additional 31 cases. Prematurity was defined as birth at 35 weeks gestation or less with a birth weight of less than 2.50 kg. Borderline prematurity was defined as birth at 35 to 36 weeks gestation with a birth weight of 2.5 to 3.25 kg. Two children were born spontaneously premature, three were born borderline, and four were delivered prematurely by cesarean section at 28, 30, 32, and 34 weeks. The overall incidence of prematurity in this sample was 7%. Seventeen subjects were delivered by cesarean section.

Maternal Age and Birth Order

Maternal age at birth was available in 115 of the 179 cases (64%). Birth order was available in 163 of the 179 cases (91%). Maternal age and birth order were available in 111 of the 179 cases (62%). Past studies have commented on the percentage of women older than 30 giving birth to children with Hirschsprung’s disease. In this study, the percentage of mothers older than 30 matched that for the general population in Massachusetts (26% of white women in this study v 26% for the state). The percentage of nonwhite mothers in this study older than 30 was 25% in comparison to 22% for the state (Table 2). The small size of this nonwhite population limited statistical analysis.

Of the white patients in this study, the percentage of first-born children (28%) compared with other positions in the birth order was found to be lower than that in the general population (41%; P < .01). Among nonwhite families, first-born children (14%) were also found at a lower frequency than that in the general population (41%; P < .05) (Table 3).

To analyze this lower-than-expected frequency, we further subdivided the study population according to type of disease (long v short segment) and maternal age. The observed frequency of first borns was always lower than the predicted frequency, although statistical significance was lost in the smallest groups.

Specifically, when the data were examined separately for long- and short-segment disease, we found that only 28% of the 132 white children with short-segment disease and known birth order were first borns. This figure compares with that of 41% for the general white population (P < .01). Only 2 of the 12 nonwhite children with short-segment disease and known birth order (17%) were first borns. This figure compares with the 41% for the general nonwhite population (.10 > P > .05). Similarly, only 5 of the 17 white children with long-segment disease for whom birth order was available were first born (29%).
This figure compares with the 41% for the general white population (.30 > .20). Neither of the two nonwhite children with long-segment disease and known birth order were first born (Table 4).

Split separately to examine birth order in relation to maternal age, this study found that among white women older than 30 years of age, only 1 child in 25 was a first-born versus 1 in 5 for the general white population ($P < .05$). Among white women younger than 30, first children (39%) were found at a lower frequency than in the general white population (48%; $20 > P > .10$). These results were mirrored in the much smaller nonwhite population. First borns to mothers less than 30 years of age in this study were 25% versus 48% for the general nonwhite population; 0 of 3 were first-born children to mothers greater than 30 years of age versus 18% for the general nonwhite population (Table 5).

**Family History of Hirschsprung’s Disease**

A family history suggestive of Hirschsprung’s disease was noted in 13 (7.3%) of the patients; 9 (5%) reported relatives specifically with Hirschsprung’s disease, and 4 reported relatives with nonspecific gastrointestinal problems such as chronic constipation or death in infancy secondary to “gastrointestinal causes.” Of the 9 definite familial Hirschsprung’s cases, 6 involved siblings of probands and 3 involved parents or other relatives.

**Table 4. Analysis of Birth Order of Children With Divisions for Short- and Long-Segment Hirschsprung’s Disease Compared With Children From the Commonwealth of Massachusetts (1969-1985)**

<table>
<thead>
<tr>
<th>Birth Order</th>
<th>Hirschsprung’s Disease (no.)</th>
<th>All Births (%)</th>
<th>Hirschsprung’s Disease (no.)</th>
<th>All Births (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>37 (28%)</td>
<td>41%</td>
<td>2 (17%)</td>
<td>41%</td>
</tr>
<tr>
<td>Other</td>
<td>95 (72%)</td>
<td>59%</td>
<td>10 (83%)</td>
<td>59%</td>
</tr>
<tr>
<td>Long-segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>5 (29%)</td>
<td>41%</td>
<td>0</td>
<td>41%</td>
</tr>
<tr>
<td>Other</td>
<td>12 (71%)</td>
<td>59%</td>
<td>2</td>
<td>59%</td>
</tr>
</tbody>
</table>

*χ² with Yates correction 8.71; $P < .01$.
*χ² with Yates correction 3.08; $10 > P > .05$.
*χ² with Yates correction 1.16; $30 > P > .20$.

**Table 5. Analysis of Birth Order of Children With Hirschsprung’s Disease by Maternal Age at the Time of Birth as Compared With Children From the Commonwealth of Massachusetts (1969-1985)**

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>White</th>
<th>Nonwhite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age &gt; 30 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>1 (4%)</td>
<td>20%</td>
</tr>
<tr>
<td>Other</td>
<td>24 (96%)</td>
<td>80%</td>
</tr>
</tbody>
</table>

*χ² with Yates correction 4.53; $P < .05$.

<table>
<thead>
<tr>
<th>Maternal age &lt; 30 yr</th>
<th>White</th>
<th>Nonwhite</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>29 (39%)</td>
<td>48%</td>
</tr>
<tr>
<td>Other</td>
<td>46 (61%)</td>
<td>52%</td>
</tr>
</tbody>
</table>

*χ² with Yates correction 2.43; $.20 > P > .10$.

Of note, 4 of the 9 patients with affected relatives had long-segment disease. This represented a disproportionate fraction of the long-segment disease in the study sample as a whole: 20% of infants with long-segment disease had affected relatives versus 3% of those with short-segment disease (23% of the cases of Zuelzer-Wilson’s disease had an affected first-degree relative). In some cases the types of diseases were discordant between relatives. Two of the children in the study were, in fact, siblings, one with long-segment disease and one with short-segment disease. In another instance, the proband had long-segment disease, the mother had short-segment disease, and a cousin had long-segment disease.

**Twins**

In this study, there were three sets of dizygotic and one set of possibly monozygotic twins. In each case, only one twin was affected. The proband in the presumably monozygotic case had short-segment disease (no HLA or ABO cross-typing was available). The dizygotic cases represented two children with short-segment and one with long-segment disease. It is of note that for the one case of monozygotic twins, the proband had skull and central nervous system abnormalities that may have been related to a neurocystopathy.

**Associated Abnormalities**

There were one or more associated congenital abnormalities in 39 of the 179 patients (22%) (Table 6). Fifteen (8.4%) of the patients had Down’s syndrome. Among the 15 cases, chromosomal analysis was available in 4. All of these showed full trisomy 21 without evidence of Robertsonian translocation. One of the four was a mosaic. One other child was found to have an incomplete chromosome number 18 by karyotypic examination.

Two patients had Dandy-Walker syndrome (a disease of cerebellar malformation). Four additional
patients had gross malformations of the skull (one with Pierre Robin syndrome and another for whom the diagnosis of Leigh's disease was being considered).

None of the children had neural crest malformations such as deafness, Waardenburg syndrome, phaeochromocytoma, neuroblastoma, or piebaldism, although such associations have been reported in the past.11-14

Fourteen (7.8%) of the patients had cardiac defects. Only 5 of these patients had Down's syndrome. Six patients had ventricular septal defects (2 Down's), 3 had tetralogy of Fallot (1 Down's), 3 had patent ductus arteriosus ([PDA] 1 Down's), 1 had endocardial cushion defect (Down's), and 1 had persistent atrioventricular canal (Down's).

Ten (5.6%) of the patients had congenital genitourinary abnormalities: 3 had bilateral inguinal hernias; 1 had cryptorchidism; 1 had a solitary kidney and bilateral inguinal hernias; 1 had bilateral inguinal hernias, hypospadias, and a double left ureter and pelvis; 1 had a urethral rectal fistula; 1 had hypospadias; and 1 had megaloureter. The only female with a genitourinary abnormality was lacking a vagina as part of the VATER syndrome (vertebral defects, anal atresia, tracheoesophageal fistula, renal and radial anomalies).

Seven (3.9%) of the patients had gastrointestinal abnormalities in addition to Hirschsprung's disease: 2 had imperforate anus, 2 had malrotation, 1 had a Meckel's diverticulum, 1 had a patent vitelline duct, and 1 had a sacral rectal fistula.

**DISCUSSION**

We report here several unrecognized demographic and pathological parameters of Hirschsprung's disease. Children with Hirschsprung's disease were found less likely to be first born. This observation was found to be statistically significant for the whole white population \( (P < .01) \) and whole nonwhite population \( (P < .05) \). This relationship was also observed among subpopulations by maternal age and type of disease (long segment v short segment). The finding was significant among white children with short-segment disease \( (P < .01) \) and among children born to white women older than 30 years of age \( (P < .05) \). This finding is of interest in light of the work of Halpin et al.18 These researchers found statistically significant elevations in maternal immunoglobulins in the rectal biopsy specimens of 3-day-old children with Hirschsprung's disease (as compared with those biopsy specimens from 3-day-old infants with other causes of neonatal intestinal obstruction). Thus, Hirschsprung's disease may share a pathogenetic mechanism with fetal Rh immunization, fetal hyperthyroidism, or fetal immune thrombocytopenia.19,20 Our observation of a decreased frequency of first-born children with Hirschsprung's disease may reflect a requirement for previous gestational antigenic stimulation.

We also find an increased association of Hirschsprung's disease with neurocrestopathies. Previous associations of Hirschsprung's disease and such neural crest malformations as deafness, Waardenburg syndrome, phaeochromocytoma, neuroblastoma, and piebaldism have been reported.11,14

In this population, approximately 8% of patients had cardiac defects. This compares with the estimated background figure of 0.5% to 1% for the general population.22,23 Only one third of these patients had Down's syndrome. If the subpopulation of

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**Table 6. Associated Abnormalities**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>22 (12.3%)</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>15</td>
</tr>
<tr>
<td>Dandy-Walker syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Gross malformation of the skull</td>
<td>4*</td>
</tr>
<tr>
<td>Clinical mental retardation</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect (2 Down's)</td>
<td>6†</td>
</tr>
<tr>
<td>Tetralogy of Fallot (1 Down's)</td>
<td>3</td>
</tr>
<tr>
<td>Patent ductus arteriosus (1 Down's)</td>
<td>3</td>
</tr>
<tr>
<td>Endocardial cushion defect (1 Down's)</td>
<td>1</td>
</tr>
<tr>
<td>Persistent atrioventricular canal (1 Down's)</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Bilateral inguinal hernias</td>
<td>3</td>
</tr>
<tr>
<td>Cryptorchidgism</td>
<td>1†</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>1</td>
</tr>
<tr>
<td>Solitary kidney and bilateral inguinal hernias</td>
<td>1</td>
</tr>
<tr>
<td>Urethral rectal fistula</td>
<td>16</td>
</tr>
<tr>
<td>Megaloureter</td>
<td>1</td>
</tr>
<tr>
<td>VATER syndrome</td>
<td>11</td>
</tr>
<tr>
<td>Blind kidney with double left ureter and pelvis; hypospadias; bilateral inguinal hernias</td>
<td>1†</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Imperforate anus, isolated</td>
<td>1</td>
</tr>
<tr>
<td>Imperforate anus in VATER syndrome with ileal atresia</td>
<td>1</td>
</tr>
<tr>
<td>Malrotation of the gut</td>
<td>2</td>
</tr>
<tr>
<td>Patent vitelline duct</td>
<td>1</td>
</tr>
<tr>
<td>Meckel's diverticulum</td>
<td>1</td>
</tr>
<tr>
<td>Sacral rectal fistula</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** Thirty-nine of 179 children with Hirschsprung’s disease had one or more associated anomalies.

*One child had Leigh's disease; one child had Pierre Robin syndrome.
†One child had hypospadias; one child had bilateral inguinal hernias; one child had Dandy-Walker syndrome and malrotation of the gut.
‡This child had Down's syndrome.
§This child also had a sacral rectal fistula.
‖This child also had imperforate anus.
¶This child also had gross malformation of the skull.
patients affected both with Down's syndrome and
Hirschsprung's disease was not considered, cardiac
defects were still present in approximately 5% of the
patients (5 to 10 times that of the background
population).

The cardiac defects fell into two major
categories. Defects of septation and PDA. If the group of pa-
tients affected with PDA (3 patients) were removed
from consideration, 6.5% of patients had a cardiac
defect involving improper septation of the heart. If
both the Down's population and patients with PDA
were removed from consideration, 3.5% of patients
still had a major septal cardiac anomaly. These
observations are of interest in view of the fact that the
neural crest is crucial to normal cardiac septation.24-27

The most common anomaly of cardiac septation
in this study was that of tetralogy of Fallot. Of the study
population of 179, 3 had tetralogy of Fallot (only 1 of
whom also had Down's syndrome). The risk of
occurrence of tetralogy of Fallot is difficult to ascer-
tain but has been estimated to approximate 1 in 2,000
live births.28 A chance occurrence of such simultane-
ously affected children among this study population
would have been predicted less than 0.07% of the
time. An association between these two disorders has
not been previously recognized.

This study also details the frequent association of
malformations of the face, skull, and central nervous
system with Hirschsprung's disease. Once again, the
association appears to be secondary to a common
neurocrestopathogenic origin. Two of the children were
observed to be simultaneously affected with Dandy-
Walker syndrome and Hirschsprung's disease. No
previous association between these two conditions has
been recognized. The Dandy-Walker syndrome
appears to occur in less than 1 in 2,000 live births.29
Hirschsprung's disease appears to occur in approxi-
mately 1 in 5,000 live births.30 A chance occurrence of
two simultaneously affected children in this study
population would be expected to occur less than 0.8%
of the time. The cerebellar hemispheres of children
affected with Dandy-Walker syndrome are abnor-
mal separately by enlarged cyst-like structures com-
prised of both leptomeningal and glial components.
This is of importance when it is recalled that the
neural crest is crucial to normal leptomeningal
formation.31,32

In this study, several children with gross malforma-
tions of the membranous bones of the face and skull
were observed. One additional patient was affected
with Pierre Robin syndrome with cleft palate, micro-
gnathia, glossophtosis, and microphthalmia. This disor-
der is also of neurocrestopathogenic origin.33,34

Previous studies have suggested that among moth-
ers of children with Hirschprung's disease, a higher
percentage of women over 30 exists than in the
general population.10 The present data do not support
this finding. In this study the percentage of mothers
older than 30 in the study population matched that
for the general population in Massachusetts.

However, this study does confirm many previously
reported demographic parameters. The male predo-
nance (77%), the rates of prematurity (7%), the
more frequent presence of short-segment disease
(89%), and the relationships of sex and familial
inheritance to length of disease have all been re-
ported.15,30,33-36 Other investigators have found that the
male-to-female ratio decreases as the length of the
involved mucosa increases.33,35,38 The present results
agree with this finding; the male-to-female ratio of 4:1
in short-segment disease decreased to 1:1 when only
long-segment disease was analyzed. In addition, 20%
of the infants with long-segment disease in this study
had a positive family history, whereas only 3% of
those with short-segment disease had a similar associ-
ation. This finding agrees with previous reports.
However, as in the past, no definitive mode of
inheritance was evident.

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