Prevalence and Association of Congenital Heart Disease with Hirschsprung's Disease

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ABSTRACT

Objective: Neurocristopathies play a role as pathogenesis of Hirschsprung's disease and congenital heart diseases (CHDs). This study seeks to identify concomitant deformities, syndromes, and/or associations associated with Hirschsprung's disease warrant evaluation for CHDs through echocardiography.

Materials and Methods: A retrospective analysis was conducted on Hirschsprung's disease patients at Siriraj Hospital between January 2006 and December 2022. Echocardiograms were performed when clinical symptoms, abnormal chest X-rays (CXR), desaturation, heart murmurs raised suspicions of cardiovascular anomalies.

Results: Among 299 Hirschsprung's disease patients, 43 (14.4%) exhibited CHDs. The sensitivity of CXR (n=268) and echocardiograms (n=51) in diagnosing CHDs was 48.8% and 100%, respectively. Predominant CHD presentations included patent ductus arteriosus (n=29), atrial septal defects (n=18), and ventricular septal defects (n=15). The presence of concomitant deformities, syndromes and/or associations associated with Hirschsprung's disease significantly heightened the likelihood of concurrent CHDs (Odds ratio = 23.56, $p < 0.001$). Patients with Hirschsprung's disease and concomitant deformities (n=28) (excluding syndromic or chromosomal abnormalities) had 1.73 times the odds of CHDs ($p = 0.262$) compared to those without concomitant deformities. Patients with Hirschsprung's disease and Down syndrome (n=34) exhibited 77.78 times higher odds of CHDs ($p < 0.001$), while those with other syndromes and/or associations (n=6) had 13.03 times higher odds of CHDs ($p = 0.005$) compared to patients lacking these conditions.

Conclusion: CHDs were identified in 14.4% of Hirschsprung's disease patients. Echocardiograms should be selectively employed in Hirschsprung's disease associated with Down syndrome, other syndromes, or concomitant deformities.

Keywords: Hirschsprung; cardiac screening; neurocristopathy; echocardiography (Siriraj Med J 2024; 76: 630-637)

INTRODUCTION

The pathogenesis of Hirschsprung's disease involves the absence of ganglion cells over a variable length of the distal gut, starting from the internal sphincter and extending proximally. This results in absent peristalsis in the affected bowel. The root cause of Hirschsprung's disease is insufficient cranio-caudal migration, proliferation and differentiation of neural crest cells within the hindgut.[1-5] Besides Hirschsprung's disease's association with neural crest differentiation, cardiac neural crest cells, a smaller distinct subset of neural crest cells, also play a crucial role in proper cardiovascular formation, including development of smooth muscles, septation of the cardiac outflow tract, valves, aortic arch artery, cardiac aortopulmonary septum,[6-10] and arterial truncus.[11,12] Studies have shown a wide-ranging prevalence of between 1.4%-17%[7-9, 13-16] of CHD in individuals with Hirschsprung's disease.

There is a controversial debate over whether all patients diagnosed with Hirschsprung's disease should undergo a heart evaluation via an echocardiogram[8,17] or if this should be limited to those presenting additional deformities, syndromes, and/or chromosomal abnormalities.[13] Despite

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reports of a high incidence of CHD in some patients with Hirschsprung's disease, the Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University does not perform routine echocardiograms for all patients with this condition.

The objectives of this study were to define the prevalence of associated CHDs in patients with Hirschsprung's disease and to evaluate which specific concomitant deformities, syndromes, and/or associations requiring further examination of associated CHDs through echocardiography. Moreover, the diagnostic index including sensitivity, specificity, positive predictive valve (PPV), and negative predictive value (NPV) of either CXR or echocardiograms in detecting associated CHD was also studied.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Siriraj (COA no. Si 843/2022). All patients with Hirschsprung's disease who were admitted for further evaluation and/or surgical treatment at Siriraj University Hospital, Mahidol University between January 2006 and December 2022 were retrospectively reviewed. Patients with Hirschsprung's disease who lacked comprehensive heart examination records (i.e., cardiac physical examination, CXR, electrocardiography and/or echocardiogram) and patients who had undergone cardiac surgery for CHD at another hospital were excluded.

In this study, CHD was defined as "a gross structural abnormality of the heart or intrathoracic great vessels potentially or actually affecting function," as defined by *Mitchell et al.*[18] This definition excludes persistent left superior vena cava, bicuspid aortic valves, mitral valve prolapse, Marfan syndrome, cardiomyopathies, and congenital arrhythmias without an associated structural heart defect (such as long Q-T syndrome). Conditions like atrial septal defects within the oval fossa, and patent foramen ovale and patent ductus arteriosus are not considered CHD within the first 14 days of life and are excluded as they are considered normal occurrences. CHDs that require percutaneous or surgical interventions are described as major.[8] Diagnosis often follows a physical examination, with further specialized tests based on clinical features. Echocardiography is used for detailed examination when a cardiovascular abnormality is suspected based on symptoms, an abnormal CXR, reduced pulse oximetry readings, or the presence of heart murmurs.

Definition of anomaly in this study

This study categorized "any associated anomalies" as instances of Hirschsprung's disease that also involved any other anomaly, either as part of a concomitant deformity, a syndrome and/or association, and/or a chromosomal abnormality. "Concomitant deformity" was defined as Hirschsprung's disease occurring alongside another congenital deformity, not including Down syndrome or any specific syndromes and/or associations or chromosomal abnormalities. A "syndrome and/or association" referred to Hirschsprung's disease coupled with a specific syndrome and/or association or any chromosomal abnormality, excluding Down syndrome which was categorized in another group.

Demographic and clinical data, including age, sex, transitional zones, CXR results, echocardiogram results, and other additional congenital anomalies were systematically collected. Quantitative data were presented as mean and standard deviation for normally distributed datasets, and as median with interquartile range for datasets not following normal distribution. The study utilized a Pearson's χ^2 test or Fisher's exact test to analyze qualitative data comparisons between the two groups, and the Mann-Whitney U test for comparing medians in quantitative data. The analysis included calculating odds ratios (OR) to assess the relationship between various exposures (anomalies, deformities, syndromes and/or associations) and the occurrence of CHD.

The diagnostic index including sensitivity, specificity, PPV, and NPV of either CXR or echocardiograms in detecting associated CHD was also studied.

Data analysis was conducted using the PASW Statistics program (SPSS for Windows, version 26.0, SPSS Inc., Chicago, Illinois, USA). A *p-value* below 0.05 was considered statistically significant.

RESULTS

In a cohort of 299 patients diagnosed with Hirschsprung's disease, 43 children (14.4%) had associated CHDs. Of these, 20 patients had major CHDs. The variety of CHD found in patients with Hirschsprung's disease is outlined in Table 1.

Chest X-rays (CXR) and echocardiograms were performed in 268 and 51 patients, respectively. The sensitivity, specificity, false positive rate, false negative rate, PPV, and NPV of both CXR and echocardiograms in detecting CHD are detailed in Table 2. The sensitivity of CXR and echocardiography in diagnosing associated CHD among patients with Hirschsprung's disease were 48.8% and 100%, respectively.

Demographic and clinical characteristics, such as age, sex, transitional zone levels, and operative

TABLE 1. Types of congenital heart disease in patients with Hirschsprung's disease.

Types of congenital heart diseases	N (%)
Acyanotic	
Left-to-right shunts;	
PDA	29 (9.7%)
ASD	18 (6.0%)
VSD	15 (5.0%)
Complete atrioventricular septal defect	1 (0.3%)
Obstructive lesions	0 (0%)
Cyanotic	
Right-to-left shunts;	
Pulmonary atresia	2 (0.7%)
Tetralogy of Fallot	1 (0.3%)
Tricuspid atresia	1 (0.3%)
Complex "mixing" lesions;	
Total anomalous pulmonary venous return	1 (0.3%)
Univentricular heart disease	1 (0.3%)
Obstructive lesions(right-sided);	
Pulmonary stenosis	4 (1.3%)
Others	
Interrupted aortic arch type B	1 (0.3%)

TABLE 2. The sensitivity, specificity, false positive, false negative, positive predictive valve (PPV), and negative predictive value (NPV) of CXR or echocardiograms in detecting associated congenital heart diseases.

	CXR (n = 268) 95% CI	Echocardiogram (n = 51) 95% CI
Sensitivity	21/43 (48.8%) (35% - 63%)	43/43 (100%) (92% - 100%)
Specificity	225/225 (100%) (98% - 100%)	6/8 (75%) (41% - 93%)
False positive	0/225 (0%) (0% - 2%)	2/8 (25%) (7% - 59%)
False negative	22/43 (51.2%) (37% - 65%)	0/43 (0%) (0% - 8%)
PPV	21/21 (100%) (85% - 100%)	43/45 (95.6%) (85% - 99%)
NPV	225/247 (91.1%) (87% -94%)	6/6 (100%) (61% - 100%)

techniques were compared between patients who did and did not have CHD, as shown in Table 3. The analysis showed no significant differences in the age at operation ($p = 0.51$), sex distribution ($p = 0.19$), transitional zone ($p = 0.37$), or the application of abdominal assisted transanal endorectal pull-through (TERPT) ($p = 0.97$) techniques between the two groups.

The prevalence of CHD detected by echocardiograms in patients with Hirschsprung's disease, alongside any concomitant deformities, syndromes and/or associations, were compared to those without any concomitant deformities, syndromes and/or associations and are shown in Table 4.

Among the 299 patients diagnosed with Hirschsprung's disease, 61 (20.4%) had associated anomalies, including

TABLE 3. Demographic data of all patients with Hirschsprung's disease, including age, sex, levels of transitional zone and operative techniques: A comparison of those with congenital heart disease and those without congenital heart disease.

Variables	All patients (n = 299)	Associated CHDs		*p* - value
		CHDs (n = 43)	No - CHDs (n = 256)	
Age of surgery (Months)				0.508
Median (Interquartile range)	3.35 (10.84)	3.68 (15.38)	3.10 (10.80)	
Sex, n (%)				0.190
Male	216 (72.2%)	27 (62.8%)	189 (73.8%)	
Female	83 (27.8%)	16 (37.2%)	67 (2.3%)	
Transitional zone, n (%)	276			0.367
Short segment	165 (55.2%)	27 (62.8%)	138 (53.9%)	
Long segment	111 (37.1%)	13 (30.3%)	98 (38.2%)	
Surgery, n (%)	296			0.974
TERPT	166 (55.5%)	24 (55.8%)	142 (55.5%)	
Abdo-assisted TERPT	86 (28.8%)	13 (30.2%)	73 (28.5%)	
Other pull-throughs	44 (14.7%)	6 (14%)	38 (14.8%)	

TABLE 4. The prevalence of congenital heart diseases detected by an echocardiogram in patients with Hirschsprung's disease who had concomitant deformities or syndromes and/or associations was compared against those without any concomitant deformities or syndromes and/or associations.

Anomalies	CHDs (n = 43) (%)	No - CHDs (n = 256) (%)	*p* - valve	Odd ratio (OR) (95% CI)
Any associated anomalies (n = 61)	33 (76.7%)	28 (10.9%)	< 0.001	23.56 (10.50 - 52.86)
Concomitant deformity (n = 28)	6 (14.0%)	22 (8.6%)	0.262	1.73 (0.66 - 4.54)
Down syndrome (n = 34)	28 (65.1%)	6 (2.3%)	< 0.001	77.78 (27.93 - 216.60)
Syndrome and/or association (n = 6)	4 (9.3%)	2 (0.8%)	0.005	13.03 (2.31 - 73.51)

concomitant deformities, syndromes and/or associations. Within this subgroup, 33 patients (54.1%) were identified having CHD. Patients with Hirschsprung's disease and associated anomalies were 23.56 times more likely to have CHD compared to those without such anomalies (76.7% vs 10.9%, OR 23.56, 95%CI 10.50 - 52.86; $p < 0.001$).

The presence of Hirschsprung's disease with concomitant deformities was noted in 28 cases, which included three cases of anorectal malformation, three of Meckel diverticulum, three of cleft lip and palate, two of central nervous system anomalies, two of gastroschisis, two of malrotation, two of hypospadias, two of limb anomalies, and one case each of microcephaly, macrocephaly, esophageal achalasia, annular pancreas, duodenal atresia, asplenia, ureteropelvic junction obstruction, bilateral undescended testis, sensorineural anomaly. Patients with Hirschsprung's patients and concomitant deformities had a 1.73-fold increase in the incidence of CHD compared to those without such deformities (14.0% vs 8.6%, OR 1.73, 95%CI 0.66 - 4.54; $p = 0.262$).

Down syndrome was identified as the most prevalent chromosomal abnormality ((34/299 (11.4%)) in patients with Hirschsprung's disease, and thus, it was classified into a distinct subgroup. Among patients with Hirschsprung's disease and Down syndrome, 28 (82.4%) had associated CHDs and 13 of these 28 patients (46.4%) had major CHDs. Patients with Hirschsprung's disease and Down syndrome were 77.78 times more likely to have CHD compared with those without Down syndrome (65.1% vs 2.3%, OR 77.78, 95%CI 27.93 - 216.60; $p < 0.001$).

Six patients with Hirschsprung's disease also had associated syndromes or associations, consisting of two cases of Mowat-Wilson syndrome, one case of DiGeorge syndrome, one case of Pierre Robin sequence, one case of Dandy-Walker syndrome and one case of Waardenberg syndrome. Patients with Hirschsprung's disease combined with these specific syndromes or associations were found to be 13.03 times more likely to have CHD compared to those without any syndromes and/or associations (9.3% vs 0.8%, OR 13.03, 95%CI 2.31 - 73.51; $p = 0.005$).

DISCUSSION

Cardiac neural crest cells contribute significantly to development of cardiac outflow tract, heart valves, aortic arch artery, cardiac aortopulmonary septum,[6-10] and the arterial truncus.[11,12] In our study, CHDs found in patients with Hirschsprung's disease aligned with the pathogenesis of cardiac neurocristopathies. Predominantly, these included acyanotic, left-to-right shunt CHD: patent ductus arteriosus (29 cases, 9.7%), atrial septal defects (18 cases, 6.0%), and ventricular septal defects (15 cases, 5.0%). Additionally, a case of hypoplastic left heart syndrome in a patient with Hirschsprung's disease was documented.[9]

Our study revealed that the sensitivities of CXR and echocardiography for diagnosing associated CHD in patients with Hirschsprung's disease were 48.8% and 100%, respectively. Echocardiography, with a 100% sensitivity, is the most effective screening tool for detecting asymptomatic CHDs, however, its precision for diagnosing specific types and conducting preoperative assessments of complex CHD is somewhat limited. While transthoracic echocardiography was efficient for diagnosing and evaluating simple CHDs, its accuracy in complex CHD cases was lower, at only 77.7%. Therefore, some patients may require additional investigations, such as computed tomography scans, cardiac magnetic resonance imaging and cardiac catheterization.[19]

The reported prevalence of CHD in patients with Hirschsprung's disease varies widely across studies, and ranges between 1.4% - 17%.[7-9,13-16] This variation has sparked debate on the appropriateness of using echocardiography to evaluate all patients with Hirschsprung's disease or for who have concomitant deformities or a syndrome or only those with chromosomal abnormality. Some research suggests that echocardiography can detect CHD in up to 45% of Hirschsprung's disease patients without cardiac symptoms, which has led to call advocating for universal echocardiographic screening in all patients with Hirschsprung's disease even if there is no concomitant deformities, syndromes or chromosomal abnormalities.[8,17] Conversely, some studies recommended echocardiography solely for patients with Hirschsprung's disease presenting with certain syndromes or other chromosomal abnormalities.[13] The discrepancies in incidence rates across studies can be attributed to differences in study methodologies and the severity of CHD.[20]

In prospective studies, mild forms of CHD, which are often asymptomatic and lack significant murmurs, tend to be detected. A prospective observational study reported an 8.3%[8] incidence of associated CHD, which is significantly higher than retrospective series or systematic literature reviews.[21-24] For instance, in the largest retrospective study[21], which examined 2,174 patients with Hirschsprung's disease, only 27 children (1.2%) were identified as having associated CHDs. The variance in reported prevalence of cardiac anomalies between prospective and retrospective studies can be attributed to that mild or absent of symptoms of associated CHDs in patients with Hirschsprung's disease could lead to misdiagnosis and/or a delayed diagnosis. Conotruncal anomalies such as transposition of the great arteries and double-outlet right ventricle, which are believed

to result from developmental issues tied to neural crest cells' critical embryological roles, were rare.[25,26]

In our retrospective study, we found that 43 out of 299 patients with Hirschsprung's disease (14.4%) also had associated CHD, indicating a higher incidence rate compared to other retrospective studies, even though echocardiograms were conducted on only 51 patients. This elevated incidence might be attributed to a higher prevalence of concomitant deformities, syndromes, and/or associations, along with a significant proportion of major CHDs (20/43 (46.5%)) in our study.

In our research, we observed that patients with Hirschsprung's disease with any associated anomalies (61/299 (20.4%)) who had either a concomitant deformity, a syndrome, and/or association, were 23.56 times more likely to have CHD compared to those without such anomalies ($p < 0.001$). These associated anomalies were categorized into three groups: 1) "concomitant deformity", defined as Hirschsprung's disease that co-occurs with another congenital deformity, excluding syndromes and/or association diseases or chromosomal abnormalities; 2) Down syndrome; and 3) a "syndrome and/or association" defined as Hirschsprung's disease with a specific syndrome and/or association or any chromosomal abnormality, excluding Down syndrome. Given these findings, it cannot be conclusively stated that all cases of Hirschsprung's disease with associated anomalies should automatically undergo echocardiographic screening for CHD without considering the distinct effects of these subgroups. Therefore, we conducted further analysis to determine whether each subgroup presents a higher risk of associated CHD and if it is suitable to perform routine echocardiographic screenings.

Hirschsprung's disease occurs as an isolated condition in approximately 70% of cases. In the remaining 30%, it is associated with various concomitant anomalies, such as gastrointestinal malformations, craniofacial and distal limb anomalies, sensorineural hearing loss, and abnormalities affecting the skin, central nervous system, genitalia, and kidneys.[6,13,27] Our study found that patients with Hirschsprung's disease who also had concomitant anomalies had a higher prevalence of CHD (6/28 (21.43%)) than patients with Hirschsprung's disease who had no concomitant anomalies (37/271(13.65%)). However, this difference in prevalence was not statistically significant ($p = 0.262$) and the odds ratio was 1.73.

Down syndrome is the most frequently occurring chromosomal abnormality associated with Hirschsprung's disease, appearing in 1% - 6% of patients.[8,28-30] Our findings show a higher prevalence of Down syndrome at 11.4% (34/299 patients), which is notably above the rate reported in, than other series. In our series, where 82.4% (28/34 patients) of patients with both Hirschsprung's disease and Down syndrome had CHD, had higher this incidence than other reported occurrences ranging between 36.1% - 62.5%.[8,13,28,31,32] The likelihood of encountering CHD in patients with Hirschsprung's disease and Down syndrome was 77.78 times higher than in those without Down syndrome ($p < 0.001$). Therefore, we recommend performing an echocardiogram for every patient with Hirschsprung's disease associated with Down syndrome. Moreover, our study suggests that a combination of Hirschsprung's disease and Down syndrome tends to present with more severe congenital heart abnormalities requiring surgical treatment compared to cases of Down syndrome alone.[8,33]

Hirschsprung's disease is linked with various syndromes and/or association,[7] such as Down syndrome (70%), Mowat-Wilson syndrome (24%), Cat eye syndrome (3%), Smith-Lemli-Opitz syndrome (2%), Turner syndrome (1%) and others such as central hypoventilation syndrome, and Goldberg-Shprintzen syndrome. The prevalence of CHD in cases of Hirschsprung's disease associated with a syndrome or chromosomal abnormality is reported at 51% (range 20% - 80%).[7] The prevalence of CHD associated with Hirschsprung's disease and each syndrome, or chromosomal abnormalities, varies[7], and is lowest in Mowat-Wilson syndrome and highest in Smith-Lemli-Opitz syndrome.[34] In our study, we observed six patients with Hirschsprung's disease and additional syndromes and/or associations: two with Mowat-Wilson syndrome, one with DiGeorge syndrome, one with Pierre Robin sequence, one with Dandy-Walker syndrome, and one with Waardenberg syndrome. Patients with Hirschsprung's disease and any associated syndrome and/or association were 13.03 times more likely to have CHD compared to those without such diseases ($p = 0.005$). Therefore, we recommend conducting an echocardiogram in each case of Hirschsprung's disease associated with a syndrome and/or association.

Limitations

1. The nature of retrospective study is the main limitation of this study which lead to selective bias whether indications and types of cardiac investigation should be conducted. A further prospective study should be performed.
2. In this study, the decision to perform echocardiographic examinations was triggered by clinical suspicions arising from symptoms, abnormal CXR, reduced pulse oximetry readings, or a heart murmur. This approach may lead to an underestimation of mild cardiac lesions.
3. The findings of this study reflect experiences of

a single institution, which serves a referral center for Hirschsprung's disease. The applicability of our results to other settings may be limited.

4. The absence of long-term cardiovascular follow-up data hindered our ability to identify mild CHDs that might manifest later in adolescence or adulthood.

CONCLUSION

In our study, Hirschsprung's disease was associated with CHDs in 14.4% of cases. CXR demonstrated a low sensitivity in diagnosing associated CHDs, indicating that echocardiograms should be considered as a more reliable diagnostic tool. However, it is not advisable to recommend echocardiograms for all patients indiscriminately.

Role of echocardiographic screenings should be applied in patients with Hirschsprung's disease associated with Down syndrome, other syndromes and/or associations, or concomitant deformities.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Author Contribution

Conceptualization: RR. Methodology: RR, CT. Formal analysis: CT. Project administration: RR, CT. Visualization: RR, CT. Writing - original draft: RR. Writing- review and editing: RR. Approval of final manuscript: all authors.

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