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Congenital Heart Defects in Hirschsprung's Disease: A Survey in Iranian Population

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ABSTRACT

Background: Hirschsprung's disease (HSCR) may be accompanied by other anomalies, including congenital heart disease (CHD), resulting in additional complications. This study was performed to evaluate the prevalence and type of concomitant CHD in hospitalized children with HSCR.

Methods: All HSCR patients (n=129) admitted to Mofid Children's Hospital in Tehran, Iran, from April 2016 to August 2019 were investigated in a descriptive cross-sectional study. Two-dimensional, M-mode and pulsed, continuous, and color Doppler provided echocardiography were applied to evaluate cardiac structure and function.

Results: CHD was observed in 48 (37.2%) cases, and the most common anomalies were Atrial Septal Defect (ASD) in 20 (15.5%), Ventricular Septal Defect (VSD) in 1 (0.8%), Patent Ductus Arteriosus (PDA) in 2 (1.6%), Tetralogy of Fallot in 3 (2.3%), ASD and Pulmonary stenosis in 2 (1.6%), ASD and PDA in 7 (5.4%), ASD and VSD in 3 (2.3%), as well as VSD and PDA in 2 (1.6%) patients.

Conclusion: Cardiac anomalies are relatively prevalent in the Iranian HSCR population participating in the present study. In addition, early echocardiographic evaluation in the setting of HSCR is recommended.

Keywords: Congenital anomaly, Congenital heart disease, Hirschsprung's disease

Introduction

Hirschsprung's disease (HSCR) or congenital aganglionosis is the most common cause of congenital intestinal motility disorder and the commonest etiology of bowel obstruction in neonates. Neural crest cells (NCC) regularly differentiate to neuronal, endocrine, craniofacial, pigmentary, and cardiac conotruncal tissue. Failure of appropriate NCC migration during early gestation leads to the absence of ganglion cells in the intestinal myenteric plexus in different lengths causing various intestinal segments involvement. Moreover, this disease affects 1 out of 5,000 live births (1, 2).

This developmental abnormality may be accompanied by anomalies in other organs due to common genetic pathways. A robust genetic basis has been proposed, and most HSCR are sporadic, although dominant and recessive inheritance, chromosomal abnormalities, and genetic syndromes have been reported. The RET gene mutation could be detected in almost half of familial and some sporadic HSCR cases (1-4), and incomplete penetrance of the phenotype has been reported. In addition, according to different studies, associated anomalies were reported in 5%-57%, and CHD (most commonly septation disorders) was observed in 5%-25% of patients (4-7).

According to limited data on cardiac involvement in HSCR, this study was conducted to evaluate cardiac anomalies in HSCR patients in Iran.

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Methods

This cross-sectional descriptive study investigated all HSCR patients admitted to Mofid Children's Hospital in Tehran, Iran (referral pediatrics hospital with university affiliation) from April 2016 to August 2019. Moreover, simple sampling with consecutive recruitment was performed. The inclusion criteria were the definite diagnosis of HSCR based on adequate pathology specimens. On the other hand, the patients with uncertain diagnoses or those who refused to participate were excluded from the study. Ultimately, 129 patients met the inclusion criteria for the study. In addition, written informed consent was taken from their parents.

Cardiac examination was performed by echocardiography using a Samsung HS70A ultrasound machine (Samsung Company, South Korea), and patients were placed in the left lateral decubitus position at rest. Images were taken using a segmental approach including subcostal four chamber and long axis, apical four chamber, parasternal long axis and short axis, as well as suprasternal long-axis views, applying PE 2-4 and PA 3-8B phased array probes to assess cardiac anatomy. Various modalities, such as 2D, as well as color and pulse Doppler, were used appropriately. Moreover, all cardiac studies were performed by the same academic pediatric cardiologist.

The data were collected in a Microsoft Excel sheet, and data analysis was performed using IBM SPSS software (version 24.0; Armonk, NY: IBM Corp). Descriptive statistical tools were used to employ means and standard deviations for continuous variables and percentages for categorical variables. The analytical statistical tests, including Student's T-test and Pearson's Chi-square test, were applied to compare continuous and categorical variables between the groups, respectively. The adjustment of the confounders and comparisons of the changes between the study groups was performed using repeated-measures analysis of variance (ANOVA) models. In addition, statistical significance was considered as a p-value of less than 0.05.

Results

This study evaluated 129 patients with documented aganglionosis confirmed by pathology report, including 46 (35.6%) girls and 83 (64.8%) boys. A total of 113 (87.6%) patients were younger and the remaining 16 (12.4%) were older than one year old. Furthermore, 23 (17.8%) and 17 (13.2%) neonates were born preterm and with low birth weight, respectively; moreover, 45 (58%) cases were delivered by cesarean section. In addition, 7 (5.4%) patients had a positive family history of HSCR. Clinical syndromes were detected in 9 (7%) patients, including Down's syndrome (n=7; 5.4%), VACTERL association (n=1; 0.8%), and Waardenburg syndrome (n=1; 0.8%). Other co-morbidities were found in 69 (53.48%) children, including head and neck (n=11; 8.6%), gastrointestinal (n=45; 34.9%), nervous system (n=5; 3.9%), skin (n=2; 1.6%), and other anomalies (n=2; 1.6%).

Congenital heart disease (CHD) was echocardiographically detected in 48 (37.2%) children; meanwhile, Patent Foramen Oval (PFO), small Atrial Septal Defect (ASD), and small Patent Ductus Arteriosus (PDA) were not considered as CHD. In addition, isolated ASD in 20 (15.5%), isolated VSD in 1 (0.8%), isolated PDA in 2 (1.6%), Tetralogy of Fallot (TF) in 3 (2.3%), ASD and Pulmonary stenosis (PS) in 2 (1.6%), ASD and PDA in 7 (5.4%), ASD and VSD in 3 (2.3%), as well as VSD and PDA in 2 (1.6%) patients were noticed. It is worth mentioning that 8 (6.2%) neonates showed other pathologies.

In patients with CHD, 30 (62.5%) and 18 (37.5%) cases were girls and boys, respectively. The male to female ratio was 1.66. Forty-four (91.7%) were younger than one year old. Moreover, 10 (20.85%) cases were born preterm, 8 (16.7%) neonates had low birth weight, and 25 (52.1%) patients were delivered by caesarian section. In addition, 1 (2.1%) neonate had a positive family history of HSCR, 6 (12.5%) cases had Down syndrome, and 30 (62.6%) patients suffered from other co-morbidities. Among the patients with CHD, it was noticed that 20 (41.7%), 1 (2.1%), 2 (4.2%), and 3 (6.3%) cases had isolated ASD, VSD, PDA, and TF, respectively. Additionally, ASD and PS, ASD and PDA, ASD and VSD, as well as VSD and PDA, were observed in 2 (4.2%), 7 (14.6%), 3 (6.3%), and 2 (4.2%) patients, respectively. It should be noted that 8 (16.7%) cases had other pathologies.

Discussion

HSCR may accompany other congenital malformations and syndromes, as well as associated cardiac defects, mainly septation disorders, which may occur in 5%-25% of patients (5-7). In this descriptive study, 129 HSCR patients (46 girls and 83 boys) were evaluated, and 87.6% of the cases were younger than one year old. Totally, 7% of the neonates were involved by a clinical syndrome, and 53.48% of the cases suffered from other co-morbidities; furthermore, CHD was detected in 48 (37.2%) patients. In

addition, among the CHD patients, 12.5% of the cases were involved by a clinical syndrome, and 62.6% of the neonates were found to have other co-morbidities.

In a prospective study, Prato et al. studied 144 HSCR cases, and they recognized associated congenital anomalies in 57.5% of the included patients in their investigation. The incidence of major CHD was 4.7% in their study, and it was more predominant in females with a 1.5/1 ratio. Meanwhile, minor CHD without significant clinical impairment was noted in 6.6% of the cases, and the most common detected lesions were septal defects. They emphasized the possibility of overtime underestimation of congenital anomalies and insisted on the importance of early genitourinary (GU) and auditory assessments in all HSCR patients, as well as central nervous system (CNS), cardiac, and ophthalmologic studies (3). Compared to the present study, a higher incidence of CHD (37.2%) was detected in the patients, 12.5% and 62.6% of whom showed Down's syndrome and suffered from other co-morbidities, respectively .

In a review article, Moore et al. reported congenital anomalies mostly in GI, CNS, as well as sensorineural and GU systems of their HSCR patients with the possibility of the susceptible genes being located on chromosomes 10 and 13. They also described the association of HSCR with Down's syndrome, sensorineural deafness, and Waardenburg syndrome. The incidence of CHD, predominantly septal defects and conotruncal anomalies, was reported as 4.99% in their study, which was far less frequent than that in the results of the present study (5).

Moreover, Prato et al. reported anomalies of the kidney and urinary tract in 25% of the HSCR patients in a prospective study, most commonly hydronephrosis and renal hypoplasia. They considered HSCR with associated urinary anomalies a novel syndrome with low intestinal phenotype penetrance. As these anomalies' incidence was 3-18 folds higher in their study, they recommended ultrasonic GU tract evaluation for all HSCR patients, although the renal function was not evaluated specifically in the patients of the present study (8).

Hasserius et al. indicated that failure to thrive and abnormal bowel function occur more commonly in the HSCR patients with CHD and recommended more considerations for HSCR children with associated CHD. As the patients who participated in the present study were mostly evaluated during the neonatal period or early infancy, the thriving condition was not evaluated in the present investigation (6).

Moreover, Tuo et al. conducted a prospective study on 133 histologically documented HSCR patients and found associated heart disease, mostly septal defects and PDA in 11 (8.3%), as well as mild aortic root dilatation in 5 (0.03%) patients. CHD requiring a percutaneous or surgical intervention was described as a major CHD. In total, 6 (4.5%) patients had a major CHD requiring surgical repair, 4 of whom had chromosomal abnormalities. Furthermore, among 11 patients with CHD, 5 (45%) and 1 (9%) cases were suffering from Down's and Turner's syndromes, respectively. They described a higher prevalence of cardiac anomalies, compared to previous studies, probably due to delayed diagnosis of milder CHD cases (7). However, the prevalence of cardiac involvement was still higher in the present study.

Moreover, in a systematic review, Duess et al. evaluated the prevalence of CHD in syndromic HSCR patients. Their results revealed the overall prevalence of CHD coexistence, mainly as septation defects, to be 3% for isolated and 51% (20%-80%) for syndromic HSCR. Therefore, they concluded a considerable prevalence of CHD in infants with chromosomal abnormalities and recommended that routine echocardiographic screening be performed for all syndromic HSCR infants (9). These findings were close to the results of the present investigation, in which Down's syndrome and other co-morbidities were detected in 12.5% and 62.6% of patients with CHD, respectively. Furthermore, in a review article, Amiel et al. found a 5% incidence rate of CHD in non-syndromic HSCR, generally ASD or VSD, which was lower than the value reported in the present study (10).

Study Limitations

A few patients were demised before confirming HSCR diagnosis; therefore, they were not evaluated echocardiographically. All syndromic patients could not be determined due to the lack of genetic tests and missed follow-up.

Conclusion

According to the relatively high prevalence of cardiac anomalies in the HSCR patient population, echocardiographic evaluation in all HSCR neonates is highly recommended, so that defects can be timely diagnosed and treated in early infancy.

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Conflicts of interest

The authors declare no conflict of interests regarding publication of this paper.

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Authors' contributions

Faezeh Ansari and Mohammad Reza Khalilian gathered the Data. Yalda Nilipour evaluated pathological specimens. Kourosh Vahidshahi performed the data analysis. Minoo fallahi and Fariba Alaei and Mastaneh Alaei wrote the manuscript. Mastaneh Alaei performed grammatical and scientific edition.

Ethics Approval

The study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR. SBMU. RETECH.REC.1398.335.).

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