Original Article

J Genet Med 2020;17(1):16-20
https://doi.org/10.5734/JGM.2020.17.1.16
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

Risk of Down syndrome in duodenal atresia and atrioventricular septal defect: Is there an ethnic difference?

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Purpose: Duodenal atresia (DA) and atrioventricular septal defect (AVSD) are well known ultrasonographic findings associated with Down syndrome. The risk of Down syndrome in fetuses with these anomalies has been reported as 30% to 40%. However, on the basis of our clinical experience, the risk of Down syndrome of DA may be lower in Korean population. To clarify this issue, we compared the risk of Down syndrome between cases with DA and AVSD.

Materials and Methods: The study population consisted of neonates who were confirmed as DA or AVSD by postnatal diagnosis. Postnatal diagnosis was made by surgery, postnatal echocardiography, or autopsy. Medical record was reviewed retrospectively.

Results: A total of 213 neonates with DA or AVSD were included: 67 cases with DA and 146 cases with AVSD. The risk of Down syndrome was 4.5% (3/67) in DA vs. 29.5% (43/146) in AVSD. When confining analysis to those whose karyotyping were not performed during antenatal period, the risk of Down syndrome were 7.9% (3/38) in DA and 35.4% (35/99) in AVSD.

Conclusion: The risk of Down syndrome in cases with DA was much lower in Korean population than previously reported risk in the literature. The significance of some antenatal sonographic markers for Down syndrome may be different according to ethnicity.

Key words: Duodenal obstruction, Atrioventricular septal defect, Down syndrome, Aneuploidy.

Introduction

Down syndrome is estimated to be 1 to 2 per 1,000 live births [1-3], usually resulting from maternal nondisjunction of chromosome 21 [4]. As Down syndrome is the most common trisomy and imposes a heavy burden on the family and the society, it has been the main focus of prenatal screening and diagnosis. The screening modalities include measurement of nuchal translucency, maternal serum screening test, cell-free DNA screening, and ultrasonographic detection of structural anomalies. Associated major anomalies of Down syndrome include central nervous system anomalies (ventriculomegaly or hydrocephalus),

Received: 19 May 2020, Revised: 17 June 2020, Accepted: 17 June 2020, Published: 30 June 2020
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Conflict of interest: The authors declare that they do not have any conflicts of interest.

cardiac anomalies, cystic hygroma, gastrointestinal anomalies (duodenal atresia [DA], esophageal atresia, tracheoesophageal fistula, or omphalocele). Some ultrasound markers such as hyperechoic bowel, pyelectasia, short long bone, or echogenic intracardiac foci can also increase the possibility of Down syndrome. Among these anomalies, cardiac defect, especially atrioventricular septal defect (AVSD), and DA are the most common ones [4].

If DA or AVSD are detected in prenatal ultrasonography, the risk of Down syndrome has been reported as 30% to 40% [5-7]. However, on the basis of our clinical experience, the risk of Down syndrome in DA may be lower in Korean population. To clarify this issue, we compared the risk of Down syndrome between cases with DA and those with AVSD.

Materials and Methods

1. Study design

In this retrospective cohort study, we included neonates who were confirmed as DA or AVSD by postnatal diagnosis at the Seoul National University Hospital between January 1999 and March 2016. The postnatal diagnosis was confirmed by surgery, postnatal echocardiography, or autopsy. The Institutional Review Board of the Seoul National University Hospital approved the clinical information for research purposes.

2. Clinical characteristics and chromosomal analysis

The clinical characteristics, type of associated congenital malformations, and the result of karyotyping were retrieved by review of medical record. In cases whose diagnosis of DA or AVSD was made in antenatal period, the decision to do fetal karyotyping was usually made by antenatal counseling. In neonates whose parents rejected to perform fetal karyotyping, or in neonates whose diagnosis of DA or AVSD was initially made in postnatal period, the decision for chromosomal analysis after birth was made according to the attending pediatrician. Neonates who died in uterus, or who died shortly after delivery and whose parents rejected the chromosome study and thus could not be evaluated with respect to the possibility of aneuploidy were excluded from analysis.

3. Statistical analysis

The results were analyzed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Proportions between groups were compared with chi-square test. A *P*-value <0.05 was considered significant.

Results

During the study period, a total of 238 neonates were suspected as DA or AVSD. Among these neonates, cases in which

Table 1. Characteristics of the study population

Characteristic	Duodenal atresia (n=67)	Atrioventricular septal defect (n=146)	*P*-value
Sex (male)	34 (50.7)	60 (41.1)	NS
Preterm delivery	16 (23.9)	10/130 (7.7)	<0.005
Termination	0 (0.0)	2 (1.4)	NS
Associated anomaly	18 (26.9)	57 (39.0)	0.084
Central nervous system	0 (0.0)	1 (0.7)	NS
Vertebral	1 (1.5)	1 (0.7)	NS
Ear, face, and neck	2 (3.0)	0 (0.0)	<0.05
Cardiovascular	9 (13.4)	55 (37.7)	<0.001
Pulmonary	1 (1.5)	1 (0.7)	NS
Gastrointestinal	7 (10.4)	2 (1.4)	<0.005
Genitourinary	4 (6.0)	0 (0.0)	<0.005
Extremities	1 (1.5)	1 (0.7)	NS
Others	3 (4.5)	1 (0.7)	0.058
Syndrome	0 (0.0)	36 (24.7)	<0.001
Heterotaxy syndrome	0 (0.0)	33 (22.6)	<0.001
Corrective surgery	66 (98.5)	128 (87.7)	<0.05
Death	1 (1.5)	31 (21.2)	<0.001

Values are presented as number (%).
NS, not significant.

postnatal final diagnosis was not DA or AVSD as suspected in antenatal period (n=17), case in which the medical record was not available (n=1), and cases in which the neonates had both of DA and AVSD (n=2) were excluded. In the remaining 218 neonates, 3 cases in which the fetus died in utero and the chromosomal result was not available because of culture failure, 1 case in which the neonates died shortly after delivery without any work up, and 1 case in which the parents rejected all kinds of work up studies were excluded from the analysis.

A total of 213 cases comprised of 67 cases of DA and 146 cases of AVSD were included in the analysis. Table 1 shows the clinical characteristics of the study population. The sex ratio and the proportion of termination of pregnancy were not different between the two groups of cases. However, the proportion of preterm delivery, rate of surgery, and the survival were different between the two groups.

Table 2. Risk of Down syndrome

Characteristics	Duodenal atresia	Atrioventricular septal defect	*P*-value
In total neonates	67	146	
Down syndrome	3 (4.5)	43 (29.5)	<0.001
In postnatal neonates[a]	38	99	
Down syndrome	3 (7.9)	35 (35.4)	<0.005

Values are presented as number only or number (%).
[a]Postnatal patients means those whose karyotyping were not performed during antenatal period.

Table 2 demonstrates the risk of Down syndrome in the two groups of cases. The risks of Down syndrome were 4.5% (3/67) in DA vs. 29.5% (43/146) in AVSD.

We also compared the risk of Down syndrome between the two groups, after confining analysis only to those whose karyotyping were not performed during antenatal period. The risks of Down syndrome were 7.9% (3/38) in DA and 35.4% (35/99) in AVSD.

Discussion

The principal findings of the study were 1) the risk of Down syndrome was lower in cases with DA than previously reported; 2) The risk of Down syndrome remained lower even when confining analysis to those whose karyotyping were not performed during antenatal period.

Table 3 shows the reported incidence of Down syndrome in DA or AVSD ranging around 28% to 51%, except the report from Taiwan with the incidence of 13%. The risks of Down syndrome were 5.4% (3/56) in DA in the current study [5-16]. Why is the risk of Down syndrome in Korean population lower than previously reported? One possible explanation might be ethnic difference in Korean or some Asian population such as Taiwanese from other ethnic groups. Actually in the current study population, the risk of Down syndromes in cases with AVSD was 30%, which was comparable to that in previous studies [6,8,9]. How-

Table 3. Reported incidence of Down syndrome in duodenal atresia or atrioventricular septal defect

Author	n	Incidence of Down syndrome	Incidence of aneuploidy
Duodenal atresia			
Singh et al. 2004 [5] (UK)	79	28 (35.4)	
Keckler et al. 2008 [7] (USA)	94	39 (41.5)	
Mustafawi and Hassan, 2008 [10] (United Arab Emirates)	77	36 (46.8)	
Choudhry et al. 2009 [11] (UK)	61	28 (45.9)	
Tsai et al. 2010 [12] (Taiwan)	30	4 (13.3)	
Current study	56	3 (5.4)	3 (5.4)
Atrioventricular septal defect			
Gembruch et al. 1991 [13] (Germany)	14		8 (57.1)
Delisle et al. 1999 [14] (Canada)	42	19 (45.2)	22 (52.4)
Fesslova et al. 2002 [6] (Italy)	82	23 (28.0)	33 (40.2)
Paladini et al. 2000 [9] (Italy)	21	9 (42.9)	10 (47.6)
Huggon et al. 2000 [8] (UK)	301	86/218 (39.4)	107/218 (49.1)
Friedberg et al. 2007 [15] (USA)	20		6 (30.0)
Berg et al. 2009 [16] (Germany)	246	77 (31.3)	129 (52.4)
Current study	138	42 (30.4)	44 (31.9)

Values are presented as number only or number (%).
AVSD, atrioventricular septal defect.

ever, the risk of Down syndrome in DA was quite lower than that in previous reports, which is about 30% [5,7,10,17].

Although DA has been thought to result from developmental failure of intestinal luminal canalization [18], the exact pathogenesis of DA remains incompletely understood. Previous studies have proposed ischemia or vascular accident as the possible etiology [19,20]. However, several evidences indicate the possibility of genetic influence on the pathogenesis. Cragan et al. [21] showed higher incidence of DA in twins than in singleton, and Gahukamble et al. [22,23] reported cases of DA occurring in two siblings and a pair of monozygotic twins. The suggestion regarding the possibility of genetic impact on the development of DA may be attributed to the lower incidence of Down syndrome in cases of DA in Korean (Asian) population. Most papers reporting higher incidences of Down syndrome in DA were originated from the data of Caucasian (Europe or North America, Table 3). Other racial/ethnic data from Asian group will help us to determine the ethnic/genetic impact on the development of DA. Indeed, several types of anomalies showed racial/ethnic differences, such as bicuspic aortic valve, esophageal atresia, type of isomerism, and other congenital anomalies [24-26].

In addition, the incidence of DA itself might be different among races or ethnicities. In the report of international clearinghouse for birth defects surveillance and research (ICBDSR), the rate of congenital small intestine atresia in Japan was 8.01/10,000 which was about three times higher than that in western countries (2.71/10,000 in Australia, 1.57/10,000 in Canada, 1.78/10,000 in Chile, 0.73/10,000 in France, 1.27/10,000 in Germany, 1.11/10,000 in United Kingdom, and 2.36/10,000 in United States) [27]. This relatively higher incidence of DA might be contributed to the different frequency of Down syndrome in DA. In other words, although DA associated with Down syndrome in Korean population is similar to that in other ethnic groups, proportion of Down syndrome in DA is lower because the incidence of DA is high.

Some may argue that the retrospective nature of the current study may predispose to the selection bias of study population. It may be that DA is easy to detect in antenatal period, resulting in increased chance of pregnancy termination, although it is usually diagnosed late 2nd or early 3rd trimester. However the different risk of Down syndrome between DA and AVSD in the current study remained significant even when confining analysis to those whose karyotyping were not performed during antenatal period.

Another possibility is the early termination of Down syndrome with DA. In Korea, the prenatal risk assessment for chromosomal anomaly is prevalent, and diagnostic test is provided in cases with positive result of screening test. Therefore, early termination according to the prenatal risk assessment for Down syndrome might be performed, before the sign of DA is apparent in ultrasound. However, only 3.9% of Down syndrome has DA, even though DA is an important ultrasonographic finding to suggest Down syndrome [28]. Therefore, early termination of Down syndrome with DA is still possible, but its impact is marginal.

The findings of the current study that the risk of Down syndrome was lower in Korean cases with DA than previous reported should be interpreted in two points of view. First, the different genetic risk of Down syndrome according to ethnicity should be taken into the consideration on the prenatal counseling in DA. This different risk can be adjusted in the diagnostic decision strategy for detection of Down syndrome. Second, other ultrasound markers for Down syndrome might need reevaluation in the risk of Down syndrome, because there is also a possibility of different risk of Down syndrome in other ultrasound abnormalities.

In conclusion, the risk of Down syndrome in cases with DA was only one-sixth to one-fourth of the risk previously reported in the literature. The significance of some antenatal sonographic markers for Down syndrome may be different according to ethnic groups.

Acknowledgements

This study was supported by SNUCM (Seoul National University College of Medicine) Foundation Research Program (800-20140525).

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