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Associated congenital anomalies among cases with Down syndrome

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ABSTRACT

Down syndrome (DS) is the most common congenital anomaly widely studied for at least 150 years. However, the type and the frequency of congenital anomalies associated with DS are still controversial. Despite prenatal diagnosis and elective termination of pregnancy for fetal anomalies, in Europe, from 2008 to 2012 the live birth prevalence of DS per 10,000 was 10. 2. The objectives of this study were to examine the major congenital anomalies occurring in infants and fetuses with Down syndrome. The material for this study came from 402,532 consecutive pregnancies of known outcome registered by our registry of congenital anomalies between 1979 and 2008. Four hundred sixty seven (64%) out of the 728 cases with DS registered had at least one major associated congenital anomaly. The most common associated anomalies were cardiac anomalies, 323 cases (44%), followed by digestive system anomalies, 42 cases (6%), musculoskeletal system anomalies, 35 cases (5%), urinary system anomalies, 28 cases (4%), respiratory system anomalies, 13 cases (2%), and other system anomalies, 26 cases (3.6%). Among the cases with DS with congenital heart defects, the most common cardiac anomaly was atrioventricular septal defect (30%) followed by atrial septum defect (25%), ventricular septal defect (22%), patent ductus arteriosus (5%), coarctation of aorta (5%), and tetralogy of Fallot (3%). Among the cases with DS with a digestive system anomaly recorded, duodenal atresia (67%), Hirschsprung disease (14%), and tracheo-esophageal atresia (10%) were the most common. Fourteen (2%) of the cases with DS had an obstructive anomaly of the renal pelvis, including hydronephrosis. The other most common anomalies associated with cases with DS were syndactyly, club foot, polydactyly, limb reduction, cataract, hydrocephaly, cleft palate, hypospadias and diaphragmatic hernia. Many studies to assess the anomalies associated with DS have reported various results. There is no agreement in the literature as to which associated anomalies are most common in cases with DS with associated anomalies. In this study we observed a higher percentage of associated anomalies than in the other reported series as well as an increase in the incidence of duodenal atresia, urinary system anomalies, musculoskeletal system anomalies, and respiratory system anomalies, and a decrease in the incidence of anal atresia, annular pancreas, and limb reduction defects. In conclusion, we observed a high prevalence of total congenital anomalies and specific patterns of malformations associated with Down syndrome which emphasizes the need to evaluate carefully all cases with Down syndrome for possible associated major congenital anomalies.

1. Introduction

Down syndrome (DS) is the most common congenital anomaly, affecting as many as one newborn out of 700 until the eighties (De Grouchy and Turleau, 1982). Afterwards, the impact of maternal age and prenatal screening changed the epidemiology of DS (Loane et al., 2013). However, despite prenatal diagnosis and elective termination of pregnancy for fetal anomalies (TOPFA), some 5000 infants with DS are born in the US each year (Cleves et al., 2007) and in Europe, from 2008 to 2012, the live birth prevalence of DS per 10,000 was 10.2 (http://www.eurocat-network.eu).

DS is the most prevalent genetic cause of intellectual disability in humans. However, infants with DS have a variety of other congenital anomalies including mostly congenital heart defects (CHD) but also other organ system anomalies (Källen et al., 1996, Torfs and Christianson, 1998). Although the excess risk of CHD among infants with DS is known, its frequency and the type and the frequency of the different categories of CHD are disputed, and estimates of the co-occurrence of other congenital anomalies among

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cases with DS are not well established. This study aims to specify the type and the frequency of associated anomalies in cases with DS.

2. Material and methods

Cases with DS for this study were derived from 402,532 consecutive pregnancies of known outcome, including live births, stillbirths, and TOPFA regardless of gestational age, registered by our registry of congenital anomalies described previously (Stoll and Roth, 1985). Minor anomalies were excluded according to EUROCAT guidelines for registration of congenital anomalies (http://www.eurocat-network.eu). Cases born in 11 maternity hospitals were examined from January 1, 1979, to December 31, 2008. The region of investigation was the city of Strasbourg, France (an urban area), and the area defined by the Departement du Bas-Rhin, in which Strasbourg is situated (a rural area). All newborns were registered within the first 8 days postpartum, as were all fetuses aborted because of anomalies discovered at prenatal diagnosis. As everywhere in our country, no delivery occurred at home in the area under study. All cases with DS and associated anomalies, live birth, stillbirth and TOPFA were examined by a clinical geneticist. Diagnoses of anomalies were confirmed by all available tests i.e. for CHD by echocardiography, cardiac catheterization, surgery and/or autopsy, for digestive system anomalies by plain radiography, abdominal echography, contrast studies, chloride sweat test, suction rectal biopsy, surgery and/or autopsy, for urinary anomalies by ultrasonographic examination of the urinary tract, voiding cystography, urethrography when dilation of the upper urinary tract, surgery and/or autopsy. Anomalies identified prenatally without postnatal confirmation were excluded. When a suspected or confirmed case was reported, information was obtained from all available records including cytogenetic files, prenatal consultation records, maternity files, neonatal unit files, autopsy reports, outpatient clinic files, pediatric files and pediatric surgery files. Surveillance for anomalies continued until 2 years of age according to the recommendations issued by academies and associations for people with DS [Bull MJ and the Committee on Genetics of the American Academy of Pediatrics, 2011; European Down Syndrome Association Health Care Guidelines for People with Down Syndrome:http://www.edsa.eu/files/essentials/edsa_essentials_2_healthcare.pdf; UK and Ireland DSMIG guidelines Down Syndrome Medical Interest Group UK and Ireland: http://www.dsmig.org.uk/publications/guidelines.html). For each case, a complete description was obtained, including photographs, radiographs, ultrasonographic examination, and karyotype (Stoll et al., 1998). However, this study was performed before the array CGH technology was available.

Cases with DS were divided into two groups: isolated when only trisomy 21 was present, and associated when one or more additional major anomalies were recognized. Major anomalies within a system were counted as one defect. For example, a case with hydronephrosis and kidney agenesis was counted once as kidney agenesis and a case with omphalocele, intestinal atresia, and malrotation was counted once as omphalocele (Lowry et al., 2013).

3. Results

During the 26-year study period, 728 cases with DS were registered representing a prevalence of 18.1 per 10,000 births. All but 48 were 47, XX or XY, +21, 20 (2.7%) were mosaic, and 28 (3.8%) were translocations mostly 14q21q or 21q21q. Of all cases with DS, 261 (36%) had no major associated anomalies and 467 (64%) had at least one major associated anomaly. The most common types of associated anomalies were cardiac anomalies, 323 cases (44% of all cases with DS), followed by digestive system anomalies, 42 cases (6%), musculoskeletal system anomalies, 35 cases (5%), urinary system anomalies, 28 cases (4%), respiratory system anomalies, 13 cases (2%), eye anomalies, 7 cases (1%), central nervous system anomalies, 6 cases (0.8%), oral clefts, 6 cases (0.8%), genital system anomalies, 4 cases (0.5%), and abdominal wall defects, 3 cases (0.4%) (Table 1). No trends in the frequency of DS were noted during the time frame of the study.

The most common CHD was atrioventricular septal defect (AVSD) which was registered in 30% of the cases with DS with CHD (Table 1) followed by atrial septal defect (ASD) (25%), ventricular septal defect (VSD) (22%), patent ductus arteriosus (PDA) (5%), coarctation of aorta (CoA) (5%), tetralogy of Fallot (TOF) (3%), and other CHD (9%).

The digestive system anomalies in cases with DS included duodenal atresia (67% of the cases of DS with digestive system anomalies), Hirschsprung disease (14%), tracheoesophageal atresia (10%), anal atresia (0.5%), and annular pancreas (0.5%) (Table 1).

The musculoskeletal system anomalies in cases with DS were syndactyly (37% of the cases with DS with musculoskeletal system anomalies), club foot (34%), limb reduction defect (14%), and polydactyly (14%).

The most common urinary anomalies in cases with DS with urinary anomalies were obstructive defects (50%).

The most common anomalies of the other systems in cases with DS included for respiratory system anomalies, lung anomalies (69%), for eye anomalies, cataracts (100%), for central nervous system anomalies, hydrocephaly (66%), for oral clefts, cleft palate (83%), for genital anomalies, hypospadias (100%), and for abdominal wall defects, congenital diaphragmatic hernia (66%) (Table 1). Prenatal diagnosis was obtained in 54% of the pregnancies. However, when the study period was subdivided into two parts, 1979–1989, and 1990–2008, prenatal diagnosis was obtained in 23% (38/193), and 66% (345/535) of the cases with DS, respectively. Pregnancy was terminated in 52.6% of the fetuses with DS.

4. Discussion

During the 26-year study period, the prevalence of DS per 10,000 births was 18.1. Sixty four per cent of the cases with DS had one or more than one associated major structural anomalies. Many studies to assess the prevalence of DS and the proportion of DS cases that are isolated compared to those that have associated anomalies have reported various results for the prevalence of DS as well as for the proportion of associated cases (Table 1). All studies shown on Table 1 were population-based except the series of Rowe and Uchida (1961), Park et al., (1977), Martin et al., (1989), Wells et al., (1994), and Papavassiliou et al., (2015). In the population-based studies, the prevalence of DS per 10,000 births ranged from 9.6 (Freeman et al., 1998) to 20.2 (Halliday et al., 2009; Morris et al., 2015) (Table 1). The proportion of cases with DS with associated anomalies varied from 32% (Morris et al., 2015) to 64% (This study) with large differences as, for example, in the more recent studies: 52% in Victoria, Australia (Halliday et al., 2009), and 37% in North of England, UK (Rankin et al., 2012), (Table 1).

In all reported series the most common associated anomalies in cases with DS were CHD. However, the percentage of CHD associated with DS varied from 26 (Källen et al., 1996) to 56 (Torfs and Christianson, 1998). The same variations in frequency were noted for different categories of CHD in cases with DS: AVSD, ASD, VSD, PDA, TOF, and CoA (Table 1). If AVSD was the most common CHD in 14 out of 18 reported studies (Table 1), among cases with DS with CHD the percentage of AVSD range from 20 (Morris et al., 2015) and 24 (Torfs and Christianson, 1998) to 52 (Pradat, 1992) and 60 (Ferencz et al., 1989). Christensen et al., (2013) studied AVSD in