Twelve-year prevalence of common neonatal congenital malformations in Zhejiang Province, China

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Background: **One of the challenges that pediatricians face when examining birth defects is to understand the trends in its occurrence and provide clues to etiology. This study was undertaken to retrospectively assess the prevalence of 10 common neonatal congenital malformations by reviewing a database of all deliveries from 28 weeks up until 7 days of birth from January 1998 to December 2009 in Zhejiang Province, China.**

Methods: **Ten common neonatal congenital malformations were selected for analysis. The incidence and the Cochran-Armitage Trend were assessed via SAS9.2. A *P* value ≤0.05 was considered statistically significant.**

Results: **Of 83 888 perinatals, 374 (4.46‰) suffered from congenital heart diseases (CHD), 77 (0.92‰) from congenital hydrocephalus, 32 (0.38‰) from intestinal atresia/stenosis, 36 (0.43‰) from anorectal malformations, 149 (1.78‰) from kidney malformations, 139 (3.31‰) from hypospadias (male), 178 (2.12‰) from orofacial clefts (OFC), 188 (2.24‰) from polydactyly, 62 (0.74‰) from syndactyly, and 269 (3.21‰) from accessory auricle anomaly. Their trend of prevalence varied as follows: CHD, *P*=0.0026; hydrocephalus, *P*=0.0042; intestinal atresia/stenosis, *P*=0.0103; anorectal malformations, *P*=0.4332; kidney malformations, *P*<0.0001; hypospadias, *P*=0.0021; OFC, *P*=0.005; polydactyly, *P*=0.0867; syndactyly, *P*=0.1941; and accessory auricle anomaly, *P*=0.0011. The upward trend was as follows: CHD (*P*=0.0026), intestinal atresia/stenosis (*P*=0.0103), kidney malformations (*P*<0.0001), hypospadias (*P*=0.0021), OFC (*P*=0.005), and accessory auricle anomaly (*P*=0.0011). The incidence of hydrocephalus (*P*=0.0042) showed a downward trend. No statistical significant trend was found in anorectal malformations (*P*=0.4332), polydactyly (*P*=0.0867) and syndactyly (*P*=0.1941).**

Conclusions: **The incidences of CHD, intestinal atresia/stenosis, kidney malformations, hypospadias, OFC, and accessory auricle anomaly have increased in the last 12 years, but the incidences of anorectal malformations, polydactyly and syndactyly remain stable. The incidence of hydrocephalus shows a downward trend.**

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Introduction

Congenital malformation is a physical defect present in a baby at birth, irrespective of whether the defect is caused by a genetic factor or by prenatal events that are not genetic. In a malformation, the development of a structure is arrested, delayed, or misdirected early in embryonic life and the effect is permanent. A major birth defect is an abnormality of an organ structure or function that results in physical disability, mental disability, or death, whereas a minor defect does not produce significant health consequences. Both major and minor defects can occur as isolated entities affecting one organ system, or as multiple defects affecting one or several organ systems.[1] About 10%-20% of the abnormalities occur in the digestive system, urinary system, and limbs, but the malformations in the nervous system and circulatory system are usually more severe, and multiple abnormalities are found in 20%-25% of cases.[2] Approximately 40% of the abnormal fetuses in pregnancy are complicated by placenta previa, polyhydramnios or oligohydramnios, and about 68% of the deformities come with genetic defects.[2]

One of the challenges that pediatricians face when examining birth defects is to identify the

trends and patterns by a longitudinal perspective study. Unfortunately, data for researchers are often incomplete because this type of information is usually rare. In 1964, the Birth Defects Monitoring Program was developed in Norway, Sweden, Hungary and other regions in order to collect the relevant information. Timely and accurate data on the prevalence of birth defects are important for the evaluation of prevention programs, identification of causes of birth defects, and as primary evidence to influence public health policy and resource allocation.[3] In the 1980s, China became involved in this birth defect surveillance system. All live or still births (with gestation of 28 weeks or more) born in participating hospitals were assessed within 7 days after delivery. Zhejiang Province, which is located in the southeastern China, is a province with rapid development of economy. Environmental factors might be related to the increasing incidence of some congenital abnormalities. In this study, we examined the prevalence of 10 common congenital malformations in the last 12 years at our hospital. This study is to understand the occurrence of the 10 malformations and to assess their potential incidences and the etiology.

Methods

Clinical data

We reviewed the data of 83 888 perinatals between January 1998 and December 2009 (from 28 weeks of gestation to a period of 7 days after birth) in our hospital. Of these perinatals, 42 001 were males and 41 887 females. Most of the pregnant women were residents of Zhejiang Province and half of them came from rural areas. According to the project of birth defect monitoring, neonatal information about congenital malformation was registered on a birth defect registration card by a midwife, either during prenatal or when the baby was born, then confirmed by a pediatrician after birth and finally reported to the data collector.

Diagnosis

Orofacial clefts (OFCs), syndactyly, polydactyly, accessory auricle anomaly, hypospadias and other visible birth defects can be diagnosed based on the definition of congenital malformation, clinical features and diagnostic criteria in *Practical Pediatric Surgery*.[2] Gastrointestinal malformations can be shown by orthostatic abdominal film and gastrointestinal imaging. Some defects such as kidney malformations, congenital heart disease (CHD) and hydrocephalus can be found by ultrasonography during the fetal period and confirmed after birth. Suspected cases can be confirmed by pediatric surgery or transferred to the children's hospital for further investigation. Prenatally diagnosed malformations were confirmed in the postnatal period before their inclusion in the database as anomalies. Some of the anomalies diagnosed after 7 days were also included in the database.

Statistical analysis

Ten types of common congenital malformations from the database registered each year were selected for analysis, including CHD (isolated cases), hydrocephalus (isolated hydrocephalus), intestinal atresia/stenosis (isolated cases including small intestine and colon), anorectal malformations (isolated cases), kidney malformations (renal hypoplasia, antenatal hydronephrosis, polycystic kidney, and renal cysts), hypospadias (exclusively male), OFC (cleft lip, cleft palate, and cleft lip with palate), polydactyly (isolated cases), syndactyly (isolated cases), and accessory auricle anomaly (isolated cases). The incidence rates and the Cochran-Armitage trend were analyzed via SAS9.2. A P value ≤ 0.05 was considered statistically significant.

Results

The numbers of newborns with different birth defects in each year are shown in Table 1. The most common defects included CHD excluding Down syndrome (374 cases), kidney malformations (149), hypospadias (139), OFC (178), polydactyly (188), and accessory auricle anomaly (269). Left-to-right shunt lesions accounted for 70% of CHD cases, most of them were ventricular septal defects (VSD) (55.6% of left-to-right shunt lesions). The number of severe CHD cases declined annually. In 65% of kidney malformation cases, antenatal hydronephrosis (≥10 mm) was noted. Cleft lip with palate, cleft lip alone and cleft palate alone accounted for about 55%, 34%, and 11% of OFC cases, respectively. Cleft lips were mostly unilateral, and only 4 cases of severe defects were bilateral. Among 188 perinatals with polydactyly, 36% occurred in the left limbs, 50% in the right limbs, and 14% in both limbs. Accessory auricle anomalies were 3-10 mm in size and localized anteriorly to the tragus.

The less common defects included hydrocephalus (77 cases), intestinal atresia/stenosis (32), anorectal malformations (36), and syndactyly (62). The patients with hydrocephalus showed a high mortality of 63.8% within 1 week after birth and the rates of preterm delivery and low birth weight were 42% and 38%, respectively. Males comprised 65% of the total cases of intestinal and anorectal malformations.

Table 1. The number of newborns with different types of malformations (*n*)

Types of malformations	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total
Congenital heart disease	8	19	19	16	16	16	34	41	43	47	51	64	374
Hydrocephalus	1	2	12	3	14	5	7	6	14	5	6	2	77
Intestinal atresia/stenosis	0	1	0	1	0	2	3	3	5	5	6	6	32
Anorectal malformations	0	1	0	3	4	3	4	5	3	3	2	8	36
Kidney abnormalities	0	6	2	3	5	13	14	12	21	23	20	30	149
Hypospadias (male only)	4	3	4	4	5	5	20	20	11	12	26	25	139
Orofacial clefts	3	3	10	13	5	9	14	19	22	25	23	32	178
Polydactyly	5	7	10	9	9	12	16	19	20	29	23	29	188
Syndactyly	1	2	2	2	7	3	7	5	4	10	10	9	62
Accessory auricle anomaly	3	8	14	13	13	8	8	57	31	37	47	30	269

Table 2. The annual incidence of the 10 types of malformations (‰)

Types of malformations	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	The average incidence
Birth number	2726	4149	5155	5121	6218	4669	7349	7677	8598	10 253	10 910	11 063	
Congenital heart disease	2.93	4.58	3.69	3.12	2.57	3.43	4.63	5.34	5.00	4.58	4.67	5.79	4.46
Congenital hydrocephalus	0.37	0.48	2.33	0.59	2.25	1.07	0.95	0.78	1.63	0.49	0.55	0.18	0.92
Intestinal atresia/stenosis	0.00	0.24	0.00	0.20	0.00	0.43	0.41	0.39	0.58	0.49	0.55	0.54	0.38
Anorectal malformations	0.00	0.24	0.00	0.59	0.64	0.64	0.54	0.65	0.35	0.29	0.18	0.72	0.43
Kidney abnormalities	0.00	1.45	0.39	0.59	0.80	2.78	1.91	1.56	2.44	2.24	1.83	2.71	1.78
Hypospadias (male only)	2.94	1.45	1.55	1.56	1.61	2.14	5.44	5.22	2.55	2.34	4.76	4.52	3.31
Orofacial clefts	1.10	0.72	1.94	2.54	0.80	1.93	1.91	2.47	2.56	2.44	2.11	2.89	2.12
Polydactyly	1.83	1.69	1.94	1.76	1.45	2.57	2.18	2.47	2.33	2.83	2.11	2.62	2.24
Syndactyly	0.37	0.48	0.39	0.39	1.13	0.64	0.95	0.65	0.47	0.98	0.92	0.81	0.74
Accessory auricle anomaly	1.10	1.93	2.72	2.54	2.09	1.71	1.09	7.42	3.61	3.61	4.31	2.71	3.21

Table 3. The trend test results of congenital malformations

Types of malformations	χ^2	*P*
Congenital heart disease	3.0112	0.0026
Congenital hydrocephalus	-2.8645	0.0042
Intestinal atresia/stenosis	2.5662	0.0103
Anorectal malformations	0.7837	0.4332
Kidney malformations	4.2305	<0.0001
Hypospadias	3.0726	0.0021
Orofacial clefts	2.8091	0.0050
Polydactyly	1.7131	0.0867
Syndactyly	1.2986	0.1941
Accessory auricle anomaly	3.2606	0.0011

The annual incidence of the malformations are shown in Table 2. The incidence of hypospadias was applied to male newborns exclusively.

The trend test results of all congenital malformations are shown in Table 3. There was a significant upward trend in the incidence of CHD (P=0.0026), intestinal atresia/stenosis (P=0.0103), kidney malformations (P<0.0001), hypospadias (P=0.0021), OFC (P=0.005), and accessory auricle anomaly (P=0.0011). Whereas the incidence of hydrocephalus (P=0.0042) showed a downward trend. In the annual prevalence of anorectal malformations (P=0.4332), polydactyly (P=0.0867) and syndactyly (P=0.1941), there was no trend of statistical significance.

Discussion

CHD, a leading cause of infant mortality associated with birth defects, can lead to chronic disability, morbidity, and increased health care costs. The incidence of CHD is associated with older maternal age, multiple gestations, race, etc.[4,5] Hoffman and Kaplan[6] reviewed 44 studies of CHD from 1955 to 2002, and pointed out that the incidence of CHD in different studies varies from about 4/1000 to 50/1000 live births. The total incidence was related to the relative frequency of VSD, the most common type of CHD. The incidence of moderate and severe forms of CHD is about 6/1000 live births and real need for treatment of severe CHD has stabilized at 2.5/1000 to 3/1000. Given the causes of variation, there is no evidence for differences in incidence in different countries or times. In our study, the incidence of CHD showed an increased trend in the past 12 years. Isolated VSD is by far the most common form. One possible explanation is that the diagnosis has been constantly improved since the application of

fetal 3-dimensional ultrasonography in pregnancy and echocardiography in neonatal nursery. Also, people tend to choose later marriage and childbearing because of education and economic changes in China in recent years. The average maternal age of CHD infants was 28.3 years in 1998, compared with 30.1 in 2009 in our study. Older maternal age has long been recognized as a risk factor for having offspring with genetic syndromes and that could be an independent risk factor for CHD.[4] The number of severe cases declined annually possibly because prenatal diagnosis of serious cardiovascular abnormalities often leads to pregnancy termination.

Of all the congenital neural tube defects (NTDs), spina bifida, anencephaly, encephalocele, and hydrocephalus are the most common ones. The first three are defects in the early embryo before neural tube closure, and hydrocephalus is usually caused by abnormal brain development, cerebral aqueduct obstruction, and Dandy-Walker syndrome.[2] In 2003, the birth prevalence of NTDs in Shanxi Province, China is among the highest in the world (13.87/1000). Folate deficiency may be an important risk factor.[7] Dai et al[8] analyzed the occurrence of congenital hydrocephalus in perinatals from 1996 to 2004 in China, and revealed a total incidence of 0.7/1000 with an increasing trend annually. The rate in rural areas was nearly 2 times higher than that in urban areas, and the incidence was higher in North China than in South China.[8] The average incidence of hydrocephalus was 0.92/1000 in our study, which was close to the incidence reported by Dai et al.[8] The annual incidence showed a trend of decrease, which is in line with a report from South Carolina, United States.[9] The use of folic acid supplements in the periconceptional period has been shown to substantially reduce the risk of occurrence. The improvement ability in prenatal diagnosis should be partly due to the decreased birth rate of hydrocephalus in Chinese perinatals.

Hypospadias is considered the most common congenital malformation in the genitourinary system. The cause of hypospadias is unknown although epidemiological studies have identified some associated factors such as genetic, endocrinologic, and environmental agents.[10] Within the period of the 1970s and 1980s, patients with hypospadias increased in Europe, and reports from two monitoring systems in the United States also showed that the incidence was doubled.[11,12] The incidence increased constantly from 1999 to 2005 in newborn babies in Southeast Asia.[13] Epidemiological studies showed that certain chemicals in the environment can interfere with the development of the urethra. Endocrine disrupting chemicals interfere with the human hormone system, leading to an abnormal endocrine feedback regulations. Environmental pollution and assisted reproductive technology may lead to an increased incidence of hypospadias.[10] We found 139 cases of hypospadias in male newborns in the last 12 years in our hospital, with an average rate of 3.3/1000, which is close to the rate of 1/200-1/300 in Europe and the United States.[14] There was an upward trend for the incidence, especially from 2004 to 2005. In 139 infants, 56% were small gestational age infants and preterm infants. About 22% of pregnant women had hypertensive disorders, suggesting a relevance to intrauterine growth restriction.[15]

Antenatal hydronephrosis can be found in 1% to 5% of pregnancies and is one of the most common birth defects. Moderate or severe antenatal hydronephrosis has a significant risk for postnatal pathology, indicating that comprehensive postnatal diagnosis should be made.[16] We found a significant increase in the incidence of renal abnormalities over the 12 years, which may be closely correlated to the use of prenatal ultrasound for screening birth defects.

Moreover, the overall rate of anorectal malformations was 0.4/1000 during the 12 years, close to the rate of 1/2162 in Canada.[17] The data from three major databases in Europe and Canada (EUROCAT,[18] British Columbia Registry,[19] Alberta Congenital Anomalies Surveillance System[17]) showed an incidence of 1/2200-1/2500. The theory of preventing anorectal malformations via daily diet has attracted the interest of researchers. A China-US collaborative project showed that daily prenatal consumption of 400 μg folic acid may reduce the risk of imperforated anus.[20]

Congenital intestinal atresia/stenosis is also a common gastrointestinal malformation that can lead to neonatal intestinal obstruction with an incidence of about 1/20 000 to 1/5000 (Males have higher rate than females).[2] The cause of the malformation is still unknown. Animal models confirmed that the damage of mesenteric vessels in fetuses may lead to an aseptic coagulation necrosis selectively limited to the intestinal mucosa and submucosa. Intense hyperemia and minimal cellular reaction in the adjacent tissue are also causes of intestinal atresia/stenosis.[21] A report[22] pointed out that it might be related to maternal glomerulonephritis in early pregnancy. In China, the incidence of maternal glomerulonephritis was 0.69/10000 in the period of 1987-1992, which was closed to the rates in other countries, with no significant differences between urban and rural areas and between males and females.[23] The average incidence in this study was 0.38/1000 in the 12 years, which was significantly increased overtime, especially from 2003 to 2009. However, the reasons for such increase remain unclear.

Our study showed that the average incidence of OFC was about 2/1000 in the 12 years, which is higher

than 1.47/1000 as reported by Gregg et al.[24] In Shanxi Province, the incidence was about 3.27/1000 in live births during the period of 2003-2004, which is among the highest worldwide.[25] In contrast to the study of Gregg et al,[24] our results revealed an increasing trend, with an average rates of 1.5/1000 in the period of 1998-2003 and 2.4/1000 in the period of 2004-2009. Although the risk factors for this disease were unknown, maternal and paternal age, abortion rate, parity and mother's occupational exposure (agricultural production and exposure to pesticides) might specifically influence this trend.[26] But the increasing incidence of OFC in our area is still unexplained and further studies are required to examine the epidemiology and risk factors of this disease in China.

Polydactyly is characterized by one or more extra fingers/toes. It can be in single or multiple forms and is usually associated with syndactyly. In our study, polydactyly and syndactyly are the isolated cases without other anomalies combined. The average incidence of polydactyly was 2.2/1000, higher than 0.94/1000 reported by Zhou et al[27] during the period of 1996-2000 in China. Polydactyly occurred more frequently in the right limbs than in the left limbs, and unilateral cases were more common than bilateral ones, which was consistent with other report.[27] The most common type of syndactyly in our study was syndactyly of the forth and fifth fingers, which affected more males than females. During the 12 years, there was no increasing trend in annual prevalence of polydactyly and syndactyly. The fact that both polydactyly and syndactyly could be found in family history suggests that genetic factors might be involved.

Accessory auricle anomaly refers to a small elevation of skin containing a bar of elastic cartilage, which is localized anteriorly to the tragus or the ascending crus of the helix. The anomaly may occur in isolation or in association with other congenital anomalies of the first arch.[2] Turkish scholars[28] reported that the incidence rate was 4.7/1000, and the rate reported by Gao et al[29] from China was 2.2/1000 during 1983-1985. Our data revealed an average rate of 3.2/1000, which was significantly increased (P<0.0001) overtime for unknown reasons. It may be credited to the improved birth defect reporting system of congenital malformations.

We summarized the prevalence of 10 common congenital malformations in 83 888 perinatals in our hospital during the period of 1998-2009. The Chinese Birth Defects Monitoring Network is a hospital-based congenital malformation registry system. Based on the fact that the hospital has the highest number of birth in Zhejiang Province, the data collected in the hospital are representative of the incidence of the province. Although some cases may be missed in the diagnosis and registration process, misdiagnosis rates may be greatly reduced with the development of technology for prenatal diagnosis. In our hospital, the birth defects monitoring program is strictly carried out, and the registration system is checked monthly by experienced staff members. As a result, the information collected can truly reflect the incidence in our region.

This study adds to a limited body of research that has used a large database in understanding neonatal congenital malformations. The results raise several questions about genital and acquired factors that may contribute to changes of the birth defects rate. But more studies are needed to compare longitudinal data to detect possible pathogenic factors and the relationship between neonatal congenital malformation and environmental changes.

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