Unusual Patterns of Neural Tube Defects in a High Risk Region of Northern China [1]

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Objective To study the prevalence of different types of neural tube defects (NTDs) in Luliang Prefecture, Shanxi province, where the prevalence of NTDs is unusually high and the correlation between NTDs prevalence and patterns. **Methods** A surveillance population-based birth defects was performed in Luliang Prefecture, Shanxi province. **Results** The results of our study showed that the prevalence of NTDs was 2-fold higher in Luliang Prefecture than in other areas of Shanxi province. Unusual patterns of NTDs were found, however, multiple NTDs were relatively common in Luliang Prefecture, accounting for over 13% of all NTDs cases in China. **Conclusion** The prevalence of NTDs is associated with its patterns.

Key words: Neural tube defects; Epidemiology; Geographic variation

INTRODUCTION

Neural tube defects (NTDs) is the most common birth defects in the central nervous system. The global prevalence of NTDs is about 1‰[1]. North Ireland has an overall NTDs prevalence rate of 6.38‰-10.92‰, while other European countries have a NTDs prevalence rate of 0.1‰-0.6‰[1], and United States has a NTDs prevalence rate of 1‰[2]. According to the data provided by International Centre for Birth Defects (ICBD) in 1998, Mexico is the highest prevalence area of NTDs with a prevalence rate of 3.48‰, and Switzerland is the lowest prevalence area of NTDs with a prevalence rate of 0.45‰. In the birth defects surveillance network covering 30 areas in 21 countries, 15 areas have a prevalence rate of less than 1.00‰, 7 areas have a prevalence rate of 1.00‰-1.49‰, 4 areas have prevalence rate of 1.50‰-1.99‰, 2 areas have a prevalence rate of 2.00‰-2.49‰, and 2 areas have prevalence rate of over 2.50‰[3]. Besides Northern Ireland, northern China, Northern India, Mexico, and South America are the high prevalence areas of NTDs. The prevalence rate of NTDs is 3.9‰-9.0‰ in Northern India[4] and 11.4‰ in Davangere and Southern India[5].

China is a country with a high prevalence rate of NTDs. However, the prevalence rate of NTDs in China varies greatly in different regions. NTDs prevalence rate was 7.25 per 1000 births in rural areas of Beijing-Tianjin in 1987[6]. Data from the Chinese Birth Defects Monitoring Program (CBDMP) between 1986 and 1987 indicate that the NTDs prevalence at birth in China is 2.7‰[7], suggesting that the NTDs prevalence rate at birth is much higher than the national average prevalence rate in the northern areas of Shanxi, Hebei, Henan, Shaanxi, Jilin, Shandong, Heilongjiang provinces and Inner Mongolia Autonomous Region. The NTDs prevalance

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Abbreviations: CBDMP: Chinese Birth Defects Monitoring Program; ICBD: International Centre for Birth Defects; NTDs: Neural Tube Defect; O/E: Observed to Expected Ratio.

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rate is 10.6‰ in Shanxi province, 6.8‰ in Hebei province, 5.8‰ in Henan province, 5.6‰ in Shanxi province, 5.3‰ in Jilin province, 5.0‰ in Shandong province, and 4.2‰ in Heilongjiang province, respectively[7].

Epidemiological studies on NTDs showed that the prevalence of spina bifida is than that of anencephaly in low risk areas than in high risk areas. Moore *et al.*[8] reported that the prevalence rate of all types of NTDs is significantly higher in the northern provinces of China (high-prevalence areas) than in Atlanta, Georgia, and USA (low-prevalence areas). However, the prevalence rate of craniorachishisis and iniencephaly is markedly higher in northern China than in other areas of China.

Based on the data and resources of the National Basic Research Program of China, we analyzed the prevalence patterns of NTDs in an unusually high prevalence area of northern China, and compared them in studied areas and low prevalence areas of China (southern China) in order to identify the unusual prevalence patterns of NTDs in high-prevalence areas and the association between NTDs prevalence patterns.

MATERIALS AND METHODS

Data

NTDs data reported here came from studies supported by the National Basic Research and Develoment Program of China. Aiming to determine the environmental risk factors of birth defects, the Institute of Population Research, Peking University/ WHO Reproductive Collaboration Center supported by the Ministry of Science and Technology, conducted a retrospective study of birth defects in ten selected townships in Luliang Prefecture, Shanxi province from July 2004 to April 2005. A population-based birth defects surveillance network comprising a network of family planning and maternal and child health at the county and township levels was established. The subjects included pregnant women with local domiciliary registration or without any local domiciliary registration but living in the study areas for more than two years, the age of their offsprings, delivered either in a hospital or at home, ranged from 20 weeks to 3 years. Pregnancy outcomes included birth defects in all live births, fetal death, stillbirth, and children under the age of 3 years. The data were collected from 1 January 2002 to 31 December 2004.

Community interview and hospital registration were used to identify cases of birth defects. As the first step of community interview, family planning workers recorded all the pregnant women and their pregnancy outcomes in the community pregnancy registration form. The cases of birth defect and the suspected cases were recorded in the community birth defects registration form. For the second step, clinicians and epidemiologists from the Capital Institute of Pediatric and Shanxi Medical University visited these communities and examined all children under the age of 3 years who were born in 2002-2004. Cases of birth defects confirmed at physical examination were recorded in the community birth defects registration form and photographs were taken. Live births not recorded before were added to the community pregnancy registration form.

Hospital registration was completed by hospitals at county and township levels. Hospital health workers recorded all live births, stillbirths, fetal deaths and pregnant terminations occurred in 2002-2004. All identified fetuses or newborns with birth defects were recorded in the hospital birth defect registration form. Clinicians and epidemiologists reviewed the medical records of maternal units and recorded the missing cases. In order to minimize the number of missing cases, medical records of maternal units were also reviewed. All identified eligible cases were recorded and confirmed at home visits. In April 2005, three villages were randomly selected for investigation of missing cases. The missing rate of live birth and birth defects was 3% and 6%, respectively.

Prevalence data of NTDs in northern and southern China were collected from the publication by US-China Collaborative Project of Neural Tube Defects Prevention[9]. This collaborative program completed a population-based surveillance of birth defects covering 30 cities, counties, and districts in Jiangsu and Zhejiang provinces in southern China, and Shanxi and Hebei provinces in northern China. The surveillance collected information about 326 874 fetuses and infants (including live births, stillbirths, and fetal deaths aged $\geqslant$20 weeks' gestation) from March 1992 to June 1994.

NTDs Classification and Coding

Cases of NTDs were defined according to the international classification of diseases 10 (ICD-10). Based on the current data, we classified NTDs into isolated and non-isolated NTDs, with the latter defined as NTDs with additional major defects. Isolated NTDs was divided into single NTDs with malformations at one site, and multiple NTDs with malformations at two or more sites. Single NTDs included anencephaly, spina bifida, and encephalocele.

Statistical Analysis

Prevalence of NTDs at birth was calculated as NTDs cases per 1000 live births plus fetal deaths

during the surveillance period. For prevalence of certain types of NTDs at birth, the numerator was the number of cases of the designated type of NTDs. The ratio of observed value to expected one (O/E) was used when the prevalence of each type of NTDs was compared in Luliang Prefecture of Shanxi province and in southern and northern China to explore the unusual patterns of NTDs in high prevalence areas. The value of O/E in an area means the ratio of observed value to the expected value. The prevalence of NTDs in southern China was used as the expected rate when the O/E in northern China and Luliang Prefecture of Shanxi province was calculated.

RESULTS

The selected area was Luliang Prefecture of Shanxi province, where the prevalence of NTDs at birth is high. In 2002-2004, 128 NTDs cases were registered in ten townships of two counties. The overall prevalence rate was 19.9‰. The prevalence rate of single, multiple, and non-isolated NTDs at birth was 14.8‰, 2.6‰, and 2.5‰, respectively (Table 1). The prevalence rate of NTDs in the survey areas was 16 times higher than the average rate of NTDs at 30 survey sites in 21 countries from 1993 to 1994, which was about 7 times higher than the Chinese national level of NTDs from 1986 to 1987, and twice the rate of NTDs in Shanxi province from 1986 to 1987[3, 7].

The prevalence rates of different types of NTDs in Luliang Prefecture of Shanxi province, northern and southern China are listed in Table 1. The O/E values of Luliang Prefecture of Shanxi province and northern China were also shown with sites in southern China as a reference. The rate of all types of NTDs was significantly higher in Luliang Prefecture of Shanxi province and northern China than in southern China. The prevalence rate of NTDs in northern China was 6.3 times as high as that in southern China, and was 22.4 times higher in Luliang Prefecture of Shanxi province than in southern China. The rate of different types of NTDs did not show the same increase as the overall rate. Multiple NTDs exhibited a greater increase than single and non-isolated NTDs with an O/E of 20.8 and 294.2 in northern China and Luliang Prefecture of Shanxi province, respectively, compared with that in southern China.

These findings suggest that distribution of different types of NTDs differs in different. (Figs. 1 and 2). The higher the overall prevalence is, the higher the proportion of multiple NTDs is. However, the proportion of single NTDs ranged 75%-80% with no significant geographic variation.

DISCUSSION

NTDs include a number of congenital malformations with various phenotypes. The classification of NTDs is important to identify its etiologic and pathogenetic mechanism. In 1976, Holmes and others[10] reported that NTDs is etiologically heterogeneous. In 1982, Khoury *et al.*[11] showed that different types of NTDs have different epidemiologic characteristics, including geographical, racial, and sex distributions. The etiologic heterogeneity exists between the upper and lower NTDs, as well as between isolated and non-isolated NTDs. One possible reason is that neural tube closure encompasses the two distinct processes with different etiologies. Spina bifida at the upper level is caused by the failure of the neural tube to close, so does anencephaly. Non-closure of the neuropore at the caudal end may play an important role in the genesis of spina bifida aperta at low levels, which represents the two consequent processes of development of neuropore and neural tube, respectively[12-13]. Since studies have suggested the differences in risk of developing upper and lower NTDs[14-16], NTDs should be classified as “isolated or non-isolated NTDs” and “upper or lower NTDs” to explore their underlying causes.

TABLE 1

Expected Ratios (O/E) for Neural Tube Defects Types in Survey Areas of Northern and Southern China, and Luliang Prefecture of Shanxi Province

	Southern China[a]		Northern China[a]			Luliang, Shanxi		
	Cases	Rate[b]	Cases	Rate[b]	O/E	Cases	Rate[b]	O/E
Single NTDs	150	0.679	467	4.406	6.5	95	14.798	21.8
Anencephaly	69	0.312	96	0.906	2.9	53	8.255	26.5
Spina Bifida	61	0.276	324	3.057	11.1	25	3.894	14.1
Encephalocele	20	0.091	47	0.443	4.9	17	2.648	29.1
Multiple NTDs	2	0.009	20	0.189	20.8	17	2.648	294.2
Non-isolated NTDs	41	0.186	99	0.934	5.0	16	2.492	13.4
Total	194	0.878	590	5.566	6.3	128	19.938	22.7

Note. [a]: Data from Pei *et al*, 2003. [b]: Rate per 1000 births. Geographic variation in the occurrence of NTDs was established. Previous studies documented an unusual distribution of NTDs types in high prevalence areas.

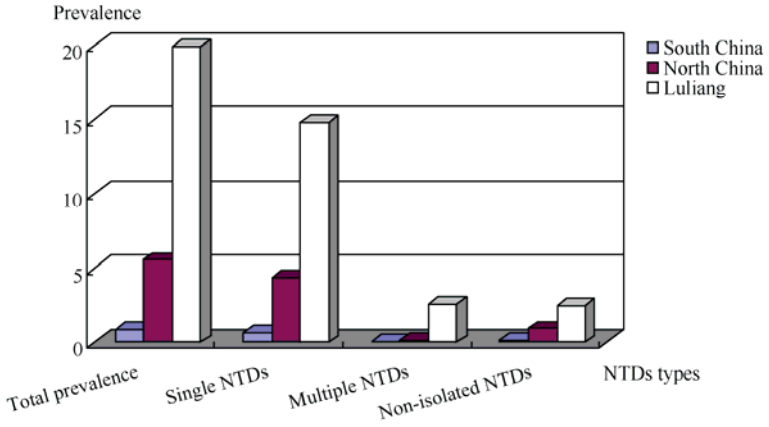

FIG. 1. Prevalence of different types of NTDs in different areas.

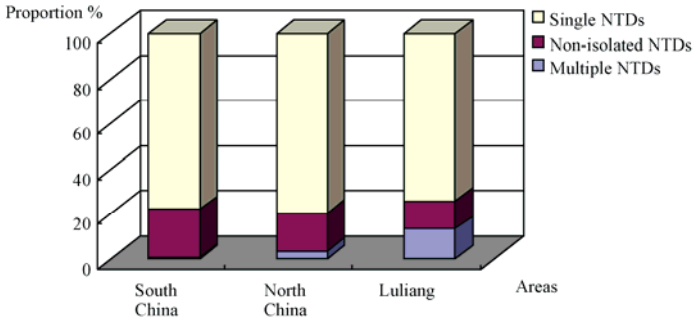

FIG. 2. Proportion of different types of NTDs.

In this study, we classified NTDs into isolated and non-isolated NTDs, and divided isolated NTDs into single and multiple NTDs. Comparison of NTDs prevalence in survey areas, low- and high-prevalence areas of China revealed unusually high prevalence rate and patterns of NTDs in Luliang Prefecture of Shanxi province. Multiple NTDs is rare in low-prevalence areas of China, accounting for 1% of all NTDs cases. However, it appears to be common in Luliang Prefecture of Shanxi province, accounting for over 13% of all NTDs cases. The prevalence of multiple NTDs in Luliang Prefecture of Shanxi province is 2.6‰, about twice the total NTDs prevalence in south Carolina[17].

Geographic variation in the prevalence of NTDs exists in different areas of different countries. Previous studies have suggested that the distribution of various types of NTDs is different in low- and high-prevalence areas, and the high-prevalence band of NTDs is present in India and Eastern Mediterranean areas, where the prevalence of anencephaly is much higher than that of spina bifida[18]. Craniorachishisis and Iniencephaly, two rare types of NTDs, are very common in northern China[8]. Similar results have been reported in UK and Ireland[19-21]. These observations show that the prevalence level of NTDs is related with the different types of NTDs, which can be used to study the pathogenesis of NTDs.

The pathogenesis of NTDs is complicated. Genetic and environmental factors play a role in the etiology and occurrence of NTDs. Khoury *et al.*[11] found that isolated NTDs is more sensitive to environmental factors, while non-isolated NTDs is sensitive to both environmental and genetic factors. Therefore, folic acid deficiency may affect isolated NTDs at a greater extent. Use of folic acid in China can prevent 84% and 41% of NTDs in high- and low-prevalence areas, respectively[22]. Community interventions with folic acid could significantly reduce the occurrence of NTDs in high prevalence areas (northern China) compared with that in low prevalence areas (southern China), indicating that the proportion of non-isolated NTDs is higher in low-prevalence areas of China. In this study, non-isolated NTDs tended to decrease with the increased prevalence of NTDs, which supports the above hypothesis. Study by Sever *et al.*[23] also

supports that genetic factors play a role in the etiology of TND in low-prevalence areas.

Since in both high- and low-prevalence areas, isolated NTDs accounted for over three quarters of all NTDs, it is necessary to explore the variations in patterns of isolated NTDs in low- and high-prevalence areas for the explaination of the geographic variation of NTDs. NTDs is a "multi-factorial" disease. According to the multi-factorial threshold model, in severely affected individuals, the higher the underlying genetic liability is, the higher the recurrent risk is. Therefore, one can assume that the prevalence of NTDs is related with the proportion of severe NTDs. Botto *et al.*[24] reported that severe NTDs tends to occur with a disproportionate frequency in high prevalence areas. It has been shown that a decreased prevalence of NTDs is associated with a significant decrease in severe forms of NTDs[25]. Craniorachishisis and iniencephaly are two types of very serious NTDs, but they are rare in low-prevalence areas and common in northern China[8]. Multiple NTDs was found in the survey area as anencephaly with spina bifida, a severe form of NTDs, which is consistent with the findings in other studies.

The etiology and mechanism of NTDs remain unknown, although significant progress has been made in the prevention of NTDs using folic acid. Since NTDs has an etiological heterogeneity, variations in areas with different prevalence rates suggest that the causes differ both in quantitaty and in qualitaty. The high prevalence and the unusual patterns of NTDs in Luliang Prefecture of Shanxi province indicate that there are some exceptional risk factors for NTDs. Further investigations should concentrate on the different patterns of NTDs in low- and high-prevalence areas.

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