Extremely High Prevalence of Neural Tube Defects in a 4-County Area in Shanxi Province, China

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BACKGROUND: In the past, northern China’s Shanxi Province has reported the highest incidence of neural tube defects (NTDs) in the world. However, little is known about the epidemiology of NTDs in this area in recent years. METHODS: Data were collected from a population-based birth defects surveillance system in 4 counties that captures information on all live births, stillbirths of at least 20 weeks’ gestation, and pregnancy terminations at any gestational age resulting from prenatal diagnosis of a birth defect. We also surveyed mothers of NTD case patients to determine their use of folic acid before and during early pregnancy. RESULTS: During 2003, 160 NTD cases were identified among 11,534 births (NTD birth prevalence = 138.7/10,000 births). The rates of anencephaly, spina bifida and encephalocele were 65.9, 58.1, and 14.7 per 10,000, respectively, and a female predominance was observed among anencephaly cases (male-to-female relative risk [RR], 0.49; 95% confidence interval [CI], 0.30–0.79), but not among spina bifida (RR, 0.90; 95% CI, 0.55–1.45) and encephalocele (RR, 1.03; 95% CI, 0.40–2.69) cases. The percentages of pregnancy termination following prenatal diagnosis of anencephaly, spina bifida, and encephalocele were 50%, 41.8%, and 35.3%, respectively. NTD birth prevalence tended to be higher among mothers aged <20 or ≥30 years (P = .06) and was markedly associated with lower levels of maternal education (P < .001). Among 143 NTD mothers, only 6 (4.2%) used folic acid supplements during the periconceptional period. CONCLUSIONS: The NTD birth prevalence rate in the study area is among the highest worldwide. Folic acid deficiency may be one important risk factor. Birth Defects Research (Part A) 76:237–240, 2006. © 2006 Wiley-Liss, Inc.

Key words: neural tube defects; prevalence; epidemiology; folic acid

INTRODUCTION

Shanxi Province, located in north central China, has been identified as the region with the highest prevalence rate of NTDs nationwide and among the highest rates reported worldwide. The high prevalence was first identified in hospital-based surveillance data from the Chinese Birth Defects Monitoring Network and was reported to be 10.55 per 1000 births during 1986 and 1987 (Xiao et al., 1990). Thereafter, NTD prevalence was reported by this surveillance system to be 10.23 per 1000 births from 1988 through 1992, and 6.09 per 1000 births from 1996 through 2000, suggesting a marked decrease in prevalence (Wang et al., 1998; Dai et al, 2002). To better estimate the current incidence and distribution of NTDs in some high-risk areas of Shanxi Province, we implemented a population-based NTD surveillance system in 4 counties in Shanxi province in 2003 and estimated the total birth prevalence of NTDs by including in the denominator all live births, stillbirths from 20 weeks’ gestational age, and pregnancy termination following prenatal diagnosis of an NTD.

MATERIALS AND METHODS

Study Location, Study Subjects, and Data Collection Procedures

The study was conducted in 4 counties (Pingding, Xiyang, Taigu, and Zezhou) located in central and southern Shanxi province, where NTD birth prevalences were higher according to local birth defects registry data. The subjects included all live births, all stillbirths of at least 20 weeks’ gestational age, and pregnancy terminations at any gestational age following the prenatal diagnosis of a major
structural external anomaly. Mothers of study subjects must have resided in the 4-county area at the time of the infant’s birth. A population-based birth defects surveillance system, which has been described previously (Li et al., 2003), was introduced in the study area in October 2002 and pilot tested for 2 months before being fully implemented on January 1, 2003. In addition, when NTD case patients were identified, health workers conducted face-to-face interviews with consenting mothers within the first week following delivery, to ascertain information concerning folic acid use before and during early pregnancy.

**NTD Case Definition and Classification**

For this analysis, we considered an NTD to be a case of anencephaly, spina bifida, or encephalocele. Two rare NTDs, craniorrhaphisis and iniencephaly, were considered to be cases of anencephaly. Spina bifida occulta was not included in the calculation of NTD prevalence. An encephalocele was classified as occurring either in isolation or in combination with other congenital malformations of various systems. Spina bifida was classified as occurring either in isolation or in combination with other congenital malformations other than with anencephaly, and encephalocele was defined as occurring either in isolation or in combination with other congenital malformations other than with anencephaly or spina bifida.

**Evaluation of Completeness of Surveillance Data**

During February 2004, we randomly selected 1 township in each of the 4 counties and conducted a retrospective survey of all births (including terminations) by interviewing all women who had been pregnant (or we interviewed 1 of their family members). In the case of a stillbirth or termination, the birth records were checked with the delivering midwife. At all suspected external defects, a professional of County Institute of Maternal and Child Health interviewed the woman and checked the case data for coding of the birth defect.

**Analysis**

We used the term “birth prevalence” as an indicator of incidence, as it is not practicably possible to determine exact incidence because the population at risk at any given time changes during gestation (Mason et al., 2005). We computed the total NTD birth prevalence rate by combining live births, stillbirths and pregnancy terminations in both the numerator and denominator, and we used the χ² test to compare rates. Significance is expressed as \( P < .05 \). SPSS version 11.5 (SPSS, Chicago, IL) was used for the analysis.

**RESULTS**

To evaluate the completeness of surveillance data in the 4 selected townships during 2004, we confirmed 30 external birth defects in these 4 townships by retrospective survey. The surveillance system reported 29 defects, all being the cases in the retrospective survey, and only 1 infant (3.3%) with polydactyly was lost to follow-up from the surveillance system. No NTD case was underreported. The total number of births in the 4 townships was 1043 in the retrospective survey, whereas the surveillance system registered 997 births, covering 95.6% of births.

During 2003, 11,534 births resulting from 11,382 pregnancies were registered in the 4 study counties. Among these, 160 NTD cases were identified (138.7 per 10,000 births). Of the 160 NTD cases, 76 (48.1%) were anencephaly, 67 (41.1%) were spina bifida, and 17 (10.8%) were encephalocele. The birth prevalences of anencephaly, spina bifida, and encephalocele were 65.9 per 10,000, 58.1 per 10,000, and 14.7 per 10,000 births. Among males, almost half of all NTD cases were spina bifida, whereas more than half of all NTDs among females were anencephaly. Overall, NTDs were less prevalent among males than among females (relative risk [RR], 0.69; 95% confidence interval [CI], 0.50–0.95); however, this was due entirely to the higher prevalence of anencephaly among females (RR, 0.49; 95% CI, 0.30–0.79). The rates of spina bifida and encephalocele were similar among males and females (RR, 0.96; 95% CI, 0.55–1.45 for spina bifida; RR, 1.03; 95% CI, 0.40–2.69 for encephalocele) (Table 1).

Among the 160 NTD cases, 31 (19.4%) were detected in live births, 57 (35.6%) were identified in stillbirths, and 72 (45.0%) were diagnosed in terminated pregnancies. Termination rates were related to the severity of the NTD: for anencephaly, 50% of pregnancies were terminated; for spina bifida, 42%; and for encephalocele, 35% (Table 2).

Table 1 shows the distribution of NTDs by maternal age and education. The mothers <20 or ≥30 years of age tended to have a high prevalence of NTDs (\( P = .06 \)). The birth prevalence of NTDs was inversely related to the level of maternal education (\( P < .001 \)). Women who had a primary school education or less had a more than 3-fold higher prevalence.

A total of 143 (89%) mothers of NTD case patients agreed to complete a face-to-face interview concerning their use of folic acid supplements. Among them, only 16 (11.2%) reported having ever used folic acid supplements, 6 (4.2%) used folic acid supplements between 3 months before and 1 month after conception, and only 4 (2.8%) used folic acid...

### Table 1

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
<th>M:F rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>Rate</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Anencephaly*</td>
<td>26</td>
<td>43.6</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>33</td>
<td>55.3</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>9</td>
<td>15.1</td>
</tr>
<tr>
<td>Total NTDs</td>
<td>68</td>
<td>113.9</td>
</tr>
</tbody>
</table>

*Not included was 1 anencephaly case whose sex was unknown.

\*\*\* \( P < .05 \).
supplements between 3 month before and 1 month after conception and lasted at least 1 month.

**DISCUSSION**

Although the incidence of the birth defects cannot be reliably estimated with existing data with respect to birth defects (Mason et al., 2005), the birth prevalence of NTDs in this study was probably a close estimate of the incidence in the study areas due to the following reasons. First, the surveillance system was population based and covered >95% of pregnant women, thus eliminating selection bias. Second, we had access to data for all pregnancy outcomes, including terminations following prenatal diagnosis of a birth defect, as well as live births and stillbirths. Third, because NTDs are clinically recognizable by providers with even limited training and because we obtained photographs and/or ultrasound records for >70% of cases and a detailed clinical description of 97% of cases, we feel that our ascertainment rate was quite high and that the diagnoses were accurate.

In this analysis on population-based surveillance for NTDs in 4 counties of Shanxi Province, China, we found that the total birth prevalence of NTDs was extremely high; female predominance existed among anencephaly cases and all NTD cases, but not among spina bifida and encephalocele cases; a higher percentage of NTDs was terminated following prenatal diagnosis; the NTD birth prevalence tended to be higher among mothers aged <20, or ≥30 years and was negatively related to maternal education. Few mothers of NTD case patients reported using folic acid supplements during the periconceptional period.

Our findings are consistent with previously reported data describing an extremely high prevalence of NTDs in Shanxi Province (Xiao et al., 1990). The total NTD rate in the study area during 2003 was ~18 times higher than that reported by the Metropolitan Atlanta Congenital Defects Program during 2001 (International Center on Birth Defects, 2003) and was not only the highest rate reported within China, but was also among the highest rate documented worldwide during the last several decades (International Center on Birth Defects, 2003).

In the present study population, the most common type of NTD was anencephaly, accounting for almost half of all NTD cases; this is consistent with other reports from China (Xiao et al., 1990) and 16 EUROCAT participating regions of Europe (EUROCAT Working Group, 1987; Sprit et al., 1990); however, other studies have reported that anencephaly was the second most common NTD, following spina bifida (Field, 1987; Himmetoglu et al., 1996; Rankin et al., 2000). The disparity may reflect a true difference in the epidemiology in different areas, which may be related to various NTD risk factors, or may also be partly attributable to differences in application of the NTD case definition. For example, craniorachischisis and encephaly, which occur with a disproportionately high frequency in areas such as northern China that have high NTD rates (Moore et al., 1997), were included as anencephaly in our study.

As reported in many other studies (Xiao et al., 1990; Elwood et al., 1992; Lary and Paulozzi et al., 2001; Rittler et al., 2004), we also observed a significant female predominance. However, in contrast to other studies that have reported a female predominance for anencephaly, spina bifida, and encephalocele (Xiao et al., 1990; Rittler et al., 2004), in our study, the higher prevalence in females was observed only for anencephaly, which occurred twice as often in females as in males; the rates of spina bifida and encephalocele were similar for both sexes. The different sex distribution between subtypes of NTDs in our study may reflect the causal heterogeneity of the NTD types (Sever and Strassburg, 1985).

In our study, almost half of pregnancies in which NTDs had been prenatally diagnosed were electively terminated. This is consistent with other studies that have reported that prenatal diagnosis substantially influences NTD surveillance (Forresier et al., 1998; Stoll et al., 2002; Bourke et al., 2005). Failure to include these cases in surveillance will result in inaccurately low NTD rates, as evidenced by a hospital-based surveillance system in China that recorded a marked decrease in NTD prevalence rate over recent years (Wang et al., 1998; Dai et al., 2002); however, only live births and stillbirths of ≥28 gestational weeks were registered in this surveillance system. This resulted in an underestimate of the total NTD birth prevalence, as pregnancies terminated before 28 weeks were not included. As prenatal diagnosis has become more widely available in recent years, the frequency of termination before 28 weeks’ gestation has also increased. We believe that the observed decline in NTD prevalence based on hospital surveillance...
data may be accounted for by prenatal diagnosis and termination of NTD-affected pregnancies.

An association of NTDs with low education was found in a U.S. study (Farley et al., 2002), and a number of studies have reported an association between low socioeconomic status and the risk for NTDs (Wasserman et al., 1998). Our data also showed a similar finding that women with low levels of education were more likely to have an NTD-affected pregnancy. In our results, NTD prevalence tended to be higher in mothers <20 and ≥20 years of age, which was similar with some reports that NTD prevalence rates were higher among infants born to mothers in younger and older age groups (Sipek et al., 2002; Forrester and Merz, 2004).

Although specific reasons for the extremely high NTD prevalence rate in Shanxi Province are not well understood, daily supplementation with 400 μg of folic acid before and during early pregnancy has been shown to be effective in reducing the occurrence of NTDs by as much as 85% in China (Berry et al., 1999). Since 1992, the China Ministry of Health has recommended that newly married women, as well as all women planning pregnancy, consume a daily supplement containing 400 μg of folic acid to prevent NTDs; the local government of Shanxi Province has had a similar recommendation since 1998. Our results suggest that despite the existence of scientific evidence on the effectiveness of folic acid supplementation in the prevention of NTDs, and its recommendation by health care authorities, only 11% of women in study area had ever taken folic acid supplements, and <5% of women took it periconceptionally according to recommendations. This is far lower than rates reported from countries such as The Netherlands, the United States, the United Arab Emirates, and Israel, which ranged from 31% to 70% of women (Bekkers and Eskes, 1999; March of Dimes, 2005; Abdulrazzaq et al., 2003; Amitai et al., 2004). In addition, food fortification with folic acid, which could ameliorate some of the problems associated with folic acid deficiency, has not yet been implemented in China. Until fortified foodstuffs reach all women of childbearing age in China, intensive efforts to educate women about the need to take supplemental folic acid before and during early pregnancy should be undertaken, particularly in high NTD risk areas in China. Moreover, additional research to identify risk factors should be conducted to provide the insight into the cause of the extremely high NTD prevalence in Shanxi province.

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