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Environmental Factors Increasing the Risk for Neural Tube Defects in the Population of Delhi (India)

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INTRODUCTION

The incidence at birth of neural tube defects (NTD) is quite different between various populations and population subgroups. In the British isles, they were found to be most common in Ireland, South Wales, and Scotland. In earlier years, they had accounted for 8 per thousand of all births in Ireland and 7 per thousand in South Wales, but somewhat over 2 per thousand only in East Anglia (Laurence 1990). In Continental Europe, still lower frequencies - less than 2 per thousand - were usually found. In Mongoloid populations, low frequencies - 1 per thousand or lower - were reported from Japan and from Southern China; among Negroids, the condition appears to be still rarer. In the North of China, on the other hand, NTD appears to be almost as common, as on the British Isles (Laurence et al., 1987; see also Moore et al., 1997). In addition to population group, factors such as social class (see also Wasserman et al., 1998) and month of conception were shown to influence incidence; among mothers from lower classes, births with NTD children were found to be at least twice as common, as in middle class families, and conceptions during February, March, and April carried an increased risk. The latter result suggests an influence of certain diseases - especially infections, for example, by the influenza virus and by "common cold" viruses. However, earlier studies to test this hypothesis had inconsistent results (Laurence, 1990). In a more recent case control study from California with unusually large series of mothers, an increased risk for an NTD pregnancy was observed in women having suffered from fever or fevrile illness episodes during the first trimester of their pregnancies (Shaw et al., 1998; See also Lynberg et al., 1994). In a study from Northern India, an influence of Dengue fever was suggested (Sharma and Gulati, 1992). Drugs increasing the risk for NTD include aminopterin, a powerful anti-folic acid agent, and valporic acid, an antiepileptic drug.

The influence of environmental factors is also suggested by a spontaneous decrease of incidence during recent decades in high-risk areas such as Southern Wales which remains significant even when pregnancies were included in statistical evaluation in which NTD had been diagnosed prenatally, and these pregnancies had been finished artificially. All these studies point to an important impact of environmental factors on the NTD risk; - mainly certain deficiencies of nutrition, but probably also diseases of the mothers.

On the other hand, observations on families point to a participation of genetic factors, as well. Among first-degree relatives of affected individuals, -sibs and children,- empirical risks were found to be about 3 - 5% (Laurence, 1990). When two children are affected, the risk for the third one is approximately doubled. Some results point to an increased risk for children from consanguineous marriages, as reported, for example, by Carter (1974) from Alexandria, where first-cousin matings were about three times as common among parents of NTD children, as in the general population. In the sultanate of Oman, NTD were also found more often in children from consanguineous matings than in the control population (Rajeb et al., 1998).

The observations suggesting a strong influence of environmental factors have led to attempts to improve the environment of mothers already before and during pregnancies. In South Wales, incidence of NTDs was reduced by about one half by a food scheme rich in vitamins and other important food ingredients (James et al., 1980; Laurence et al., 1980,1983). Placebo-controlled nutrition studies with folic acid supplementation, (Smithells et al., 1976; Laurence et al., 1981), as well as a comprehensive international study (MRC Vitamin Study Research Group 1991) showed a high protective effect of folic acid supplementation. A number of candidate genes are being discussed that might influence susceptibility for shortage of folic acid and NTD risk (Barber et al., 1999). A risk factor for NTD appears to be an increased plasma homocystein level which is reduced by folic acid (Brower et al., 1999). Another factor enhancing NTD risk appears to be an increased body mass index of the mother (Shaw et al., 1996; Källén, 1998; Waller et al., 1991; Watkins et al., 1996; Werler et al., 1996; Haddow et al., 1995; Schindler, 1998). A prospective study from Mainz (Germany) on 20 248 pregnancies showed an increased risk of maternal obesity for a number of malformations (Queisser-Luft et al.1998).

A few studies in Indian populations point to a relatively high incidence of NTD in some Indian population groups,- especially in Sikhs (Hall et al., 1988; Stevenson et al., 1966; Verma, 1978). Moreover, the frequency of NTDs among sibs of NTD probands was found to be twice as high, as in sibs of non-Sikh patients (Hall et al., 1988), pointing to a stronger participation of genetic factors. However, a relatively high incidence of NTDs was also found in South India (Kulkarni et al., 1989).

The high differences in incidences between various populations as well as a strong influence of environmental factors suggested a systematic attempt to study the role of specific environmental influences on the occurrence of NTDs in an Indian population. In the great majority of Indian families - especially women - the degree of environmental hardships was expected to be much higher than in Western populations. Therefore, stronger effects were regarded to be possible. Therefore, we performed a case-control study comprising a great number of environmental parameters.

METHODS AND MATERIALS

This study has been restricted to mothers of children who were born with neural tube defects,- spina bifida in the great majority of cases. The series did not contain cases with anencephaly. Names and addresses of mothers were compiled from the records of three hospitals in Delhi: Kalavati Saran Hospital attached to Lady Hardinge Medical College; Safdarjung Hospital; and Lok Nayak Jai Prakash Narain Hospital. The study was restricted to mothers living in the Metropolitan Area of Delhi (about 10 million). The total number of addresses initially collected was 1296; 400 of these turned out to be mothers of children with various types of microcephaly. This leaves about 900 mothers of NTD children. During the course of tracing the addresses it was found that about 40% of these mothers had actually come to Delhi from other places for hospitalization, and had given a local address to the hospital, while about 45% of the recorded persons could not be traced at all despite repeated visits to their recorded addresses. Finally, only 97 mothers could be traced who had a NTD child. Then, the principal investigator (A.K.K.) met the mothers in their homes, explaining the purpose of this study. Finally, 85 of the 97 women consented to co-operate. Then, they were visited repeatedly, and the planned examinations were performed. In a pilot study, the questionnaire to be used was pretested to 20 mothers in different ways in order to test the most efficient way of extracting the relevant data. Moreover, for all these mothers, a control mother was located who never had a NTD child. These controls were selected to come from a not too different socio-economic category, and from the same caste and age group. From these controls, exactly the same data were recorded, and the same examinations were performed, as in the NTD mothers. The questionnaire contained information on various aspects of socio-economic status of the family, and education of the mother. Diet was assessed in great detail (see below). Data on marriage and reproductive history included consanguinity; age at menarche; diseases immediately before and during pregnancy with the affected child; number and sex of children; age of the mother at their birth; child mortality before, during and after birth; age and cause of children's death. In addition, a full set of anthropological measurements was taken. For collecting all these data, between three and eight visits per woman were necessary. The data were taken by three anthropology students who were supervised by A.K.K., with R.Ch. acting as medical counselor. Patients and mothers with doubtful diagnoses were visited additionally by F.V. Examinations were performed during 1994 and 1995. 75 of the NTD children were born between 1981 and 1995, 25 of them 1981 - 1985, 28 in the years 1986 - 1990, and 22 in the years 1991 - 1995. 10

children were born between 1971 and 1980. Statistical evaluation was done by K. Schlaefer, German Cancer Research Center (DKFZ), Heidelberg.

RESULTS

The data were statistically evaluated using standard methods. Matched evaluation was performed. Significant or suggestive differences between mothers of NTD children and control mothers were found in the following variables:

1. The NTD mothers married somewhat later but had more conceptions and more live births (Tables 1 a-c). These differences were significant.
2. The age of the mother at birth of the affected child was slightly higher than that of the control mother at birth of the control child (P = 0.001; Table 2). This was exclusively due to the fact that there were more mothers between 28 and 39 years of age among the case mothers (odds ratio (OR) based on comparison of mothers up to 23 years of age, and higher than 23 years at birth of the affected child, was found to be 3.0; 95 per cent confidence interval 1.6 - 5.7.
3. A short time before and especially during pregnancy with the NTD child, their mothers suffered from more, - and especially more severe,- diseases (Table 3). The odds ratio between NTD and control mothers (all categories of diseases together) was found to be 3.3. Classification into the four categories (0-3) was performed by F.V. "blind"; i.e. he did not know whether the individual case history was that of a NTD or a control mother. The following diseases were classified as "severe": Hospitalized because of high blood pressure, in one case combined with icterus and swelling of legs;

Table 1a: Age of the mother at marriage

	Case mothers (n=84)	*Control mothers (n=85)*
Mean:	18.9 years	17.7 years
Median:	18 years	18 years
Test of independence (Wilcoxon)	p = 0.0146	
Odds ratio_{MH} (basis: 13-18 years):	2.0 (95%-CI: 1.04-3.7, p = 0.038, sig.)	
Odds ratio_{paired} (basis 13-18 years):	3.2 (95%-CI: 1.3-7.9, p = 0.0138, sig.)	

Table 1b: Number of conceptions

	Case mothers (n=85)	*Control mothers (n=82)*
Mean:	4.4. conceptions	3.7. conceptions
Median:	4 conceptions	4 conceptions
Test of independence (Wilcoxon)	p = 0.0347 sign.	
Odds ratio_{MH} (basis: 0-4 conceptions)	1.8 (95%-CI: 0.97-3.4), p= 0.061) n.s.	
Odds ratio_{paired} (basis 0-4 conceptions)	2.7 (95%-CI: 1.14-6.5) p = 0.0239 sign.	

Table 1c: Number of live births

	Case mothers (n=85)	*Control mothers (n=85)*
Mean:	3.8 births	3.1 births
Median:	4 births	3 births
Test of independence (Wilcoxon)	p = 0.017 sig.	
Odds ratio_{MH} (basis: 0-4 births)	2.2 (95%-CI: 1.06-4.4) p = 0.33, sign.	
Odds ratio_{paired} (basis 0-4 births)	3.0 (95%-CI: 1.2-7.6, p = 0.0198, sign.	

Table 2: Age of mother at birth of NTD child

	Case mothers (n=85)	*Control mothers (n=67)*
Mean:	25 years	22.5 years
Median:	24 years	22 years
Test of independence (Wilcoxon)	p = 0.0013 sig.	
Odds ratio_{MH} (basis: 0-4 births)	3.0 (95%-CI: 1.6 - 5.7) p = 0.001, sign.	
Odds ratio_{paired} (basis 0-4 births)	5.4 (95%-CI: 2.1 - 14.0) p = 0.0005, sign.	

Table 3: Number of mothers suffering from a disease shortly before or during pregnancy with the NTD or control child

	Mothers of NTD-children	*Control mothers*	*Sum total*
Not sick	52	78	130
Mild disease	11	5	16
Moderate disease	12	0	12
Severe disease	10	2	12

Test of independence: $p < 0.0001$, sign.

severe icterus in a second case; genital bleeding in two instances; anemia (severe) in two cases, in one of them combined with continuous vomiting; sometimes combined with pain in the lumbar region. One mother was hospitalized, receiving oxygen and glucose infusions. Moderate diseases included fever for some weeks during early pregnancy, sometimes combined with coughing and, in one case, with exanthema (7 study participants); high blood pressure in two cases, in one of them combined with vomiting; light genital bleeding in the first months of pregnancy; severe vomiting requiring glucose infusions; edema of legs and arms. The following complaints were classified as mild: cystitis during pregnancy; light swelling of legs; arthritis with pain in the back; treatment because of bronchial asthma; increased blood pressure without complications; frequent use (3x per diem) of chewing tobacco. Among the controls, there were only two cases of category 3, one of them with increased blood pressure and blood sugar. Category 2 (moderate disease) was not represented; in category 1 (mild disease), there were one case of light swellings of hand and feet, two cases of increased blood pressure, one chronic anemia, and one case of Tbc in earlier years but inactive at the time of pregnancy.

4. The number of consanguineous marriages in parents of NTD children was low in the entire sample (6 of 85 in NTD mothers; 1 of 85 in control mothers). The difference found was not significant (Fisher's exact test: $p = 0.12$). But it is in the direction expected if there would be a higher incidence of NTD children from consanguineous marriages.
5. Among the NTD children, there were many more boys than girls (Sex ratio M:F = 1.7). This contradicts results from many other studies in Western populations (Laurence 1990), and also in Palestinian women registered in a hospital in Jerusalem (Dudin 1997). In these studies females used to be more common among NTD patients. This discrepancy might have more social than biological reasons.
6. The following parameters were recorded to assess the socio-economic status of the families: Annual income of household; annual per capita income; family property (residential; agricultural; commercial); luxury items such as cars, scooters, TV sets, washing machines; refrigerators, and some others. Moreover, information on professional status of both parents was collected: Schooling, occupation, status of work. In none of these parameters, a significant difference between families of NTD patients and controls could be discovered.. Location of the household in a slum region had a strong protective effect when compared with the semi-urban/urban region as basis: (OR = 0.274, 95%-Confidence Interval (CI): 0.09 - 0.88, $p = 0.022$). No tendencies of a difference were observed for the anthropological measurements. The following measurements were taken: Height, weight, chest girth and inspiration and expiration, arm and wrist girth; hip and calf girth; subcutaneous fat (triceps, biceps, and calf); head measures; arm span and arm length; leg length. Moreover, the body mass index (BMI) was calculated. Mean of the BMI (85 case mothers): 22.2; 85 controls: 22.0. Median in case and control mothers: 21; test of independence (Wilcoxon): $p = 0.5757$ (n.s.) Odds ratio paired (Basis 19 - 24 years) 0.7 (95% - CI:: 0.3 - 2.2; $p = 0.34$) Odds ratio (Mantel-Haenszel) (Basis 19 - 24 years): (95% - CI: 0.3 - 2.2, $p = 0.162$). Both ORs are not significant. But 5 patient mothers and 6 control mothers only had a BMI of 30 or above. - All anthropological measures failed to show any consistent differences. There was no tendency toward obesity or an increased body mass index in NTD mothers, - in distinction to reports in Western populations (See above). But obesity is very rare in the population group studied in Delhi.

The significant variables "Age at Marriage",

Age at Birth of NTD-Child" and "Location of Household" were then evaluated together in a multivariate model, using paired and non-paired approaches. Although the model with all three variables included had the highest probablity (p= 0.0002) in both paired and non-paired analyises, only "Age at Birth of NTD-Child" and "Location of Household" remained significant in the non-paired analysis. Further evaluations revealed a highly significant correlation between location of the household in a slum and marriage at an earlier age which is compatible with general experiences (Pearson correlation coefficient=-0.20848, p = 0.0064). "Age at Marriage" lost its significance in the non-paired analysis. In the paired analysis its odds ratio slightly decreased from 3.2 (univariate evaluation) to 2.9 (multivariate evaluation) (Table 4). As the data was matched by caste the paired analysis might not reveal the true effect of the relation of location of the household in a slum and the risk of getting a NTD-child. The results of the non-paired analysis might be more reliable. A possible explanation for the effect of living in a slum, marrying at lower age and the reduced risk of having a NTD-child might be explained by underreporting: It is very likely that the chance of a NTD-child to survive in a slum region is less good than compared to a NTD-child born in a semi-urban or urban region. It is also very likely that due to social pressure the birth of a NTD-child will not be reported to the interviewer

Table 4: Multivariate Analysis of Age at Marriage, Age at Birth of NTD-Child, and Location of Household*

Multivariate Analysis - Non-paired Model p-Value: 0.0002			
Variable	*OR*	*95%-CI*	*p-Value*
Age at Marriage	1.5	0.8 - 2.9	0.2516
Age at Birth of NTD-Child	3.2	1.6 - 6.2	0.0007
Location of Household	3.9	1.1 - 13.6	0.0299

Multivariate Analysis - Paired Model p-Value: 0.0001			
Variable	*OR*	*95%-CI*	*p-Value*
Age at Marriage	2.9	1.1 - 8.1	0.0377
Age at Birth of NTD-Child	5.5	2.0 - 15.0	0.0008
Location of Household	5.2	1.05 - 25.7	0.0435

* For a better comparison of the magnitude of the effects of the three variables the basis of the variable "Location of Household" has been switched, i.e. "Slum" has been taken as basis and "Semi-Urban/Urban" as "exposure".

by a mother living in a slum region. This would explain that a young age at marriage and living in a slum have both a "protective" effect.

Caste, religious group, and migration history did not show influence on NTD incidence. Here, however, it should be remarked that about half the NTD mother-control pairs had been matched also for caste; therefore, a possible caste effect could be hidden. Moreover, the sample did not contain any Sikh women; in Sikhs, incidence of NTDs had been described to be higher than in other Indian populations.

Many parameters were assessed to discover any differences between NTD and control mothers in nutrition, - for example, annual per capita kitchen expenditure; vegetarian vs. non-vegetarian; amount of milk consumed/day by the mother; number of full and half meals in a week; frequency of pulses (a kind of lentils), vegetables, and fruits; source of water supply. The NTD mothers had a higher consumption of meals per day and a higher number of full meals Moreover, more of them lived in semiurban areas. They used slightly more domestic milk supply.

DISCUSSION

This study confirms earlier indications that diseases of mothers during the first months of pregnancy increase the risk for neural tube defects in children. Here, infections with fever appear to be especially dangerous. A significantly higher age at marriage in NTD mothers might possibly point to a slightly slower sexual maturation. On the other hand, number of conceptions and live-born children before the affected child was higher in NTD mothers than in the controls, possibly pointing to a higher degree of exhaustion, especially of mothers living under slum conditions. A significantly higher mean maternal age at the of birth of the NTD child is rather unusual when compared with data from other populations. It is caused by a higher incidence of NTD among children of mothers in the older age group (28 - 39 years). The difference in consanguinity rate, though not significant, is in the direction expected if recessive mutants would be involved. It does not contradict the observation of Kulkarni et al.(1989), Rajab et al.(1998), and Carter (1974) who found higher consanguinity rates in parents of NTD children. The hypothesis suggested by various studies in Western countries that certain nutritional deficiencies enhance the NTD risk was not confirmed in this population. There were no consistent differences between patient and control mothers in any of the variables studied - socioeconomic status, anthropological measurements, including the body mass index, or nutrition. But the diet in this population is relatively rich in vegetables; this might provide a sufficient amount of folic acid for pregnant women. A higher consumption of dairy products by NTD mothers, when compared with a higher body mass index reported in some other populations, might possibly indicate a negative influence of fat intake; but this is a shaky hypothesis.

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KEY WORDS Spina bifida. Pregnancy Complications. Nutrition. Social Factors. Consanguinity.

ABSTRACT Maternal factors possibly influencing incidence of neural tube defects (NTD) were studied in 85 mothers from Delhi who had given birth to a NTD child in comparison with 85 mothers matched for age group and caste who had no NTD children. Mothers of NTD children had been affected significantly more often with diseases - especially infections with fever - during pregnancy. They were married slightly (not significantly) more often to a close relative; age at marriage was significantly higher among mothers of NTD children, and total number of conceptions and live births was also significantly higher. Maternal age of these NTD mothers at birth of the NTD child was somewhat increased, as well; this was due to a higher frequency of mothers in the highest age group (28 - 39 years). There was no influence of variables related to nutrition such as family income, dietary habits or anthropological measurements. The hypothesis derived from studies in Western populations that certain dietary deficiencies may increase the risk of women to give birth to NTD children was not confirmed, and the often reported negative influence of obesity of the mother (enhanced body mass index) was not observed, since maternal obesity is very rare in the population studied. In an urban Indian population, diseases during pregnancy, - especially infections with fever, - appear to be the most important environmental risk factors.

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