NEURAL TUBE DEFECTS IN THE ASIR REGION OF SAUDI ARABIA

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Background: The aim of the study was to determine the incidence of neural tube defects (NTD) among admissions at a regional referral hospital in Saudi Arabia, compare trends over several years and note any influence of prenatal folic acid treatment.

Patients and Methods: For every NTD admission into the newborn unit of Asir Central Hospital, during the period January 1995 through December 1998, data were collected on the infant and mother and input into a programmed form.

Results: During the period, 64 infants were admitted with NTDs, giving an incidence of 0.78/1000 births in the region. The yearly admission frequency (4.5%-8%) was closely the same (average 6.6%) over the 4-year period (P>0.05). The sex incidence was equal and the major lesions were myelomeningocele (70%) and encephalocele (23%). Thoracolumbar (44.4%) and lumbosacral (40%) regions were the most common sites of spina bifida; encephalocele were largely occipital (93%). A majority (87%) of infants with myelomeningocele were hydrocephalic at birth. Fifty percent of the infants were offspring of consanguineous marriage (first and second cousins). Eighty-three percent of the mothers attended antenatal care, but 70% of these reported late (from the 12th week of pregnancy). Only 25% of the 64 mothers were on folate supplementation during the affected pregnancy and no mother received preconceptional folic acid supplementation.

Conclusion: The incidence of NTD in the region appears to be non-declining over the years, a situation which is at variance with experience in Western countries. There is a need to consider an intensive approach to periconceptional folic acid supplementation for Saudi women. Genetic counseling may also be important.

Key Words: Neural tube defects, Saudi infants, maternal folic acid status.

There has been a large variation in the incidence of central nervous system defects in different parts of the world and at different periods.1-4 In the Western countries, neural tube defects (NTD) form a large but diminishing proportion of all major congenital malformations.1,4,5 The causes of NTD include drugs, malnutrition, chemicals, radiation and genetic aberrations which may affect the normal development of the central nervous system in utero. The lesions of NTD include spina bifida, encephalocele, anencephaly, dermal sinus, diastematomyelia, tethered cord, syringomyelia, and lipoma of the conus medularis.

In a previous survey on congenital malformations in the Asir Central Hospital (ACH) in the years 1992 through 1995, NTD alone constituted about 25% of the major structural defects among babies admitted into the neonatal intensive care unit.6 This study is aimed at determining the pattern, trend in the frequency and the possible etiological correlates of NTD among infants admitted to the ACH from January 1995 through December 1998. Regarding etiology, the main focus was on folic acid status of the women. It is expected that the findings of this study may assist in planning and evaluation of health care programs, towards reducing the prevalence of this very handicapping condition. The NICU of Asir Central Hospital is purely a referral unit; the hospital has no Obstetric and Gynecological service of its own. The ACH is the only hospital in Asir Region (population about 2 million) that provides neurosurgery and pediatric/neonatal surgical services.

Neural tube defects are malformations of the developing brain and spinal cord occurring during the third to the fourth week of gestation. Myelomeningocele is a protrusion of the spinal cord into a sac on the back through deficient axial skeleton with variable dermal covering. Meningocele is a cystic dilatation and protrusion of the meninges of the caudal neural tube without involving the spinal cord, and covered by intact skin. Encephalocele is a herniation of the brain tissue outside the cranial cavity due to mesodermal defect occurring at the time or shortly after anterior neural tube closure. Anencephaly is a hemorrhagic and degenerated neural tissue exposed through uncovered cranial opening extending from the lamina terminalis to the foramen magnum due to failure of anterior tube closure.

Patients and Methods

All newborns referred with NTD to the NICU of ACH during the period January 1995 through December 1998 constitute the subject of this survey. For every consecutive case of NTD admitted, data were obtained and entered into...
a programmed form. Data of interest included date of birth, sex, antenatal care, previous infants with NTD, folic acid medications taken before and during pregnancy, and consanguinity between the parents. Other data included the type and site of lesion and the associated congenital malformations.

The neurosurgery and the orthopedic (if indicated) services were involved in management of these patients. Before any surgical correction of the defect, the patients had plain radiographs, ultrasonography and computerized tomography of the spine and brain done to determine the extent of the lesion and detailed involvement of the spine and brain. Every patient also had ultrasonography of the abdomen and radiographs of the hips and the lower limbs done to exclude associated congenital anomalies, including hip dislocation. Other investigative procedures were carried out as indicated. In view of the poor prognosis, it was not our policy to conduct any major investigative procedure on anencephalic infants. Management of the cases was as indicated, including ventriculoperitoneal shunting in those with hydrocephalus. Figures on total deliveries in the population were obtained from the Ministry of Health.

Chi-square or Fisher’s exact test was applied whenever necessary. The *P*-value of 0.05 or less was considered statistically significant.

**Results**

During the period under consideration, a total of 977 infants were admitted to the NICU. Of this number, 64 or 6.6% were admitted as a result of NTD. These were made up of 32 males and 32 females, a sex ratio of 1:1. The total number of deliveries in the region during the 4-year period was 82,176, giving an incidence of 0.78/1000 births. The yearly admission rate for NTD ranged from 4.5%-8%, thus suggesting that the frequency of infants born with NTD in the population was fairly similar every year (*P*>0.05).

Thirty-two (50%) of the 64 offspring were derived from consanguineous marriage (first and second cousins) and the parents were not related in the other 50%. Family history of NTD among the siblings of the infants in the series was negative.

Fifty-three (83%) of the mothers in the series had attended antenatal care (ANC); 11 or 17%did not. Sixteen (30%) of the 53 mothers who attended ANC reported at the medical institutions within the first 12 weeks while 37 (70%) of them presented for ANC from the 12th week of pregnancy.

Sixteen or 25% of the 64 mothers were on folic acid supplementation during the affected pregnancy, while the bulk of 48 (75%) were not. This implies that only 16 or 30% of the 53 women who attended antenatal care received folic acid. None of the mothers were on folic acid supplementation before the onset of the affected pregnancy.

Myelomeningocele (45 cases or 70%), and encephalocele (15 cases or 23.4%) were the major types of NTD encountered in the study (Table 1). Others were anencephaly (3 cases or 4.7%) and meningocele (1 case or 1.6%). Except among the anencephalics, in which the females predominated, the sex incidence of each of the anomalies was approximately the same. The 3 anencephalics were infants born and brought from home; none was a referral from a health institution.

Among the 45 infants with myelomeningocele, the most commonly affected sites were thoracolumbar (20 or 44.4%) and lumbosacral (18 or 40%), contributing 84.4% of the lesions, with the lumbar (4 cases), thoracic (2 cases) and cervical (1 case) sites contributing only 15.6% of the lesions (Table 2). All the cases of thoracolumbar, lumbosacral and lumbar myelomeningocele were complicated with flaccid paraplegia, and incompetent anal and urinary sphincters. The infant diagnosed with meningocele (herniated lumbosacral defect covered by normal skin) had no detectable neurological deficit. Among the 15 newborns with encephalocele, 14 were occipital and 1 was frontal.

Hydrocephalus was present in 39 (86.7%) of 45 infants with myelomeningocele at birth, but only 13 (33.3%) of these 39 cases had obvious and demonstrably large head size (>95th percentile) at birth, while the majority (26 or 66.7%) were born with normal head size appropriate for gestational age.

The most common associated birth defects encountered in these infants (Table 3) included talipes equinovarus in 21 patients and dislocation of the hip in 16 patients. Other associated anomalies were imperforate anus, congenital adrenal hyperplasia, polydactyly, Down syndrome, microphthalmia, and Meckel Gruber syndrome. Some of the patients had more than one associated anomaly.

**Discussion**

Since the ACH is the only referral tertiary center for newborns who require specialized investigative procedures and neonatal surgery in the Asir Region, the authors assume that the NICU had pooled the bulk of babies born with NTD in the area. The findings of this study can therefore provide some reasonable and helpful clues regarding the pattern of NTD in the population.

The study identifies that over the 4-year period, an average of about 7% of the overall neonatal admissions into the NICU was due to NTD, and this condition constituted 4.5%-8% of the yearly neonatal admissions, with no tendency towards a decline. The incidence of the malformation in the region is 0.78/1000 births. Indeed, this is very likely to be an underestimation of the true situation since, presumably and understandably, infants with anencephaly and spina bifida occulta were not referred from the peripheral hospital for obvious reasons. Neural tube defects therefore appear to contribute significantly to the perinatal morbidity and long-term handicap in the Asir population. This experience is at variance with the situation in Scotland5,14 and the USA,1 where a downward trend in the incidence of NTD is being observed. This difference is attributed largely to the general health and nutritional status of the community and is due only in part to the easily
Nevertheless, the highest incidence of anencephaly is in Great Britain and Ireland and the lowest in Asia and Africa. Other countries have intermediate rates of incidence. Anencephaly occurs six times more in whites than in blacks and females are more often affected than males, as was seen in our study.

In our patients, the thoracolumbar region was the most common site, which agrees with the Western trend of distribution. In contrast, the lumbosacral region seems to be predominantly involved in North American babies.

We observed that 87% of infants with myelomeningocele were already hydrocephalic at birth, which is comparable with the international figure of 85%-90%.

Though other birth defects such as talipes equinovarus deformity and congenital dislocation of the hip were rampant among our patients, they do not, by convention, form part of the syndrome of NTD. Generally, the study reveals multisystemic lesions among a significant number of the infants, thus reflecting the polymorphous nature of congenital malformation. Other authors have also reported a similar experience of a multiplicity of other congenital anomalies, some of which are outside the central nervous system, in association with neural tube defect.

A high incidence of NTD in a community is known to be genetic in its etiological relationship. Perhaps this phenomenon applies to this study population in which as high as 50% of the affected infants were offspring of consanguineous marriage. Consanguineous marriage is an important correlate of congenital malformation. In a study of congenital malformation in Al Qassim City in the Eastern Region of Saudi Arabia, 54% of patients with congenital malformation were of consanguineous marriages. In a study conducted on 3103 Saudi females, the consanguinity rate in different provinces ranged from 52% to 68%, with the highest prevalence in first-cousin marriages. In the Asir region, the frequency of consanguineous marriage is 54%. Since high rates of inbreeding influence the frequency of genetic defects and congenital malformation, it becomes paramount to mount a genetic counseling campaign in this society.

The risk of recurrence to siblings following the birth of a fetus or baby with NTD is around 5%, but we did not record any case of NTD in the siblings of our index cases.

The etiology of NTD has been proven to be closely related to folic acid deficiency. Folic acid deficiency can be the most obvious cause if there is a sustained high frequency of NTD in the population. Folic acid supplementation is therefore a well-recognized preventive measure against NTD, with a dramatic decline in the incidence of NTD noted in many parts of the world. Though poor attendance of antenatal clinics is a well-known phenomenon among Saudi women in the Asir Region, a majority (83%) of the subjects in the present study had attended antenatal care, but only 30% of those who attended received folic acid supplementation. It is disturbing that a majority (70%) of the mothers who attended antenatal care reported after 12 weeks of pregnancy when the neural tube formation would have been completed, hence the folic acid would have produced no desired effect. However, true prevention of NTD is only possible through adequate early supplementation.

### Table 1. Types of lesions and sex distribution among 64 newborns with neural tube defects.

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>No. of males</th>
<th>No. of females</th>
<th>Total (%)</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelomeningocele</td>
<td>24</td>
<td>21</td>
<td>45 (70.3)</td>
<td>0.67</td>
<td>0.41</td>
</tr>
<tr>
<td>Meningocele</td>
<td>0</td>
<td>1</td>
<td>1 (1.6)</td>
<td>–</td>
<td>1.0</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>8</td>
<td>7</td>
<td>15 (23.4)</td>
<td>0.09</td>
<td>0.77</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>32</td>
<td>64 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Site of lesions of myelomeningocele (n=45).

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracolumbar</td>
<td>20 (44.4)</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Cervical</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Total</td>
<td>45 (100)</td>
</tr>
</tbody>
</table>

### Table 3. Associated anomalies in patients with NTD.*

<table>
<thead>
<tr>
<th>Neural tube defect</th>
<th>Associated anomaly</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelomeningocele</td>
<td>Talipes equinovarus</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Congenital DH</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Congenital AH</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Imperforate anus</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Klippel-Feil syndrome</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Down syndrome</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Polydactyly</td>
<td>1</td>
</tr>
<tr>
<td>Eencephalocoe</td>
<td>Meckel-Gruber syndrome</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Imperforate anus with hypospadias</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Right inguinal hernia with hyoplastatic radii</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cleft palate with polydactyly</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Down syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

DH=dislocation of the hip; AH=adrenal hyperplasia; *the patient with meningocele had no associated anomaly and the 3 patients with anencephaly were not screened for associated lesions.
possible with periconceptional folic acid supplements.\textsuperscript{1,7,22}

The progressive decline in incidence of NTD in the developed world is not only due to antenatal diagnosis and termination but also due to improved standard of living and folic acid supplementation before and during pregnancy. The critical period during which the neural tube closes is from day 21 to day 26 of gestation. Current United Kingdom recommendation is that all women who plan to become pregnant should take folate supplementation 4 mg daily from one month before conception to the 12th week of pregnancy.\textsuperscript{1,5} Alternatively, the American Academy of Pediatrics Committee on Genetics has endorsed the United States Public Health Services’ recommendation that all women of childbearing age in the USA who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs.\textsuperscript{21} With the approval by the Food and Drug Administration, grain products fortified with folic acid have been introduced in New England for use of pregnant women.\textsuperscript{4}

As a routine, health institutions in the Asir region do offer folic acid to pregnant women who attend the ANC in their establishments, but this study has revealed that the compliance is extremely poor. Personal communication reveals that there is no policy on preconceptional folate supplement use, and so far the practice in the Asir Region is purely post-conceptional folate supplementation. It is most likely, therefore, that the non-declining frequency of NTDs among our study population may be closely related to the poor folic acid status of the pregnant women in this area.

The discoveries made in this study stress the need for mass education on the value of planned pregnancy, early attendance of ANC and the relevance of periconceptional folic acid. The Ministry of Health of Saudi Arabia should consider a more intensive approach to folate supplementation for women in view of the non-declining trend of NTD in this region. Also, given the high incidence of consanguineous marriage among the affected population, there may be some wisdom in advocating the use of genetic counseling for neural tube defects.

References

23. Recommendation of the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;4 (RR-14):1.