Neural Tube Defects at Siriraj Hospital, Bangkok, Thailand-10 Years Review (1990-1999)

Pornswan Wasant MD*,
Achara Sathienkijkanchai MD*

*Division of Medical Genetics, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objectives: *Neural tube defects (NTDs), (including anencephaly, meningomyelocele and encephalocele), are among the most common birth defects, with high associated mortality and morbidity. NTDs occur in 1-5 per 1,000 births, with marked geographic and ethnic variations. However, there are few data concerning the incidence, associated anomalies, treatment and outcome of NTDs in Thailand. The objective of this study is to analyze data on NTD cases from 1990-1999 at Siriraj Hospital, a hospital with 18,000-20,000 deliveries annually.*

Material and Method: *A retrospective chart review of patients with NTDs who were born at or referred to Siriraj Hospital 1990-1999 was performed.*

Results : *During the 10 year period we examined, there were 115 patients with NTDs treated in the Department of Pediatrics as well as in other Departments at Siriraj Hospital. The incidence of NTD is 0.67 per 1,000 births. The sex distribution was equal among NTD cases, 55 (48%) females, 59 (51%) males and one (1%) unidentified sex. Isolated NTDs accounted for 105 (91%) cases, and 10 (8.7%) had at least 1 other structural anomaly such as cleft lip/palate, imperforate anus, amniotic band sequence, or ambiguous genitalia. Among all NTD cases, there were 55 (48%) with myelomeningocele, 45 (39%) with anencephaly, and 14 (12%) with encephalocele . Seventeen (15%) cases died; among these, 7 (41% of deaths) died in utero, 8 (47% of deaths) died in the early neonatal period, and 2 (12%) died after 1 year of age. Regarding treatment, 95 surgical corrections, 47 excisions and repairs, 45 excisions and VP shunts, 1 laminectomy and 2 club feet corrections were performed.*

Conclusions: *In this hospital-based study of 115 patients with NTD, we found an incidence of 0.67/1000 births; however, as this was a hospital-based study, the community incidence is likely higher. Most cases were isolated NTDs, and almost half of NTDs were meningomyelocele. There was a high rate of mortality. Further studies are warranted to better elucidate the health burden from NTDs in Thailand. Public health interventions aimed at increasing the periconceptional consumption of folic acid should be implemented or enhanced to reduce the incidence of NTDs in Thailand.*

Keywords: *Neural tube defects, Anencephaly, Encephalocele, Meningomyelocele, Folic acid supplementation*

J Med Assoc Thai 2005; 88(Suppl 8): S92-9
Full text. e-Journal: *http://www.medassocthai.org/journal*

Neural tube defects (NTD) are among the most serious and common birth defects which result in infant mortality, morbidity, and disability. These include anencephaly, meningomyelocele and encephalocele with an incidence of 1-5 per 1,000 births [1,7,10], showing marked geographic and ethnic variations (Fig. 1). The incidence is highest in the UK and lowest in Japan, but is markedly higher if all affected embryos were to be considered[1]. In the USA, the Centers for Disease Control (CDC) reported over 4,000 pregnancies per year [2-3,6-7], and estimated that 300,000 to 400,000 newborns worldwide were affected by spina bifida each year [1-3].

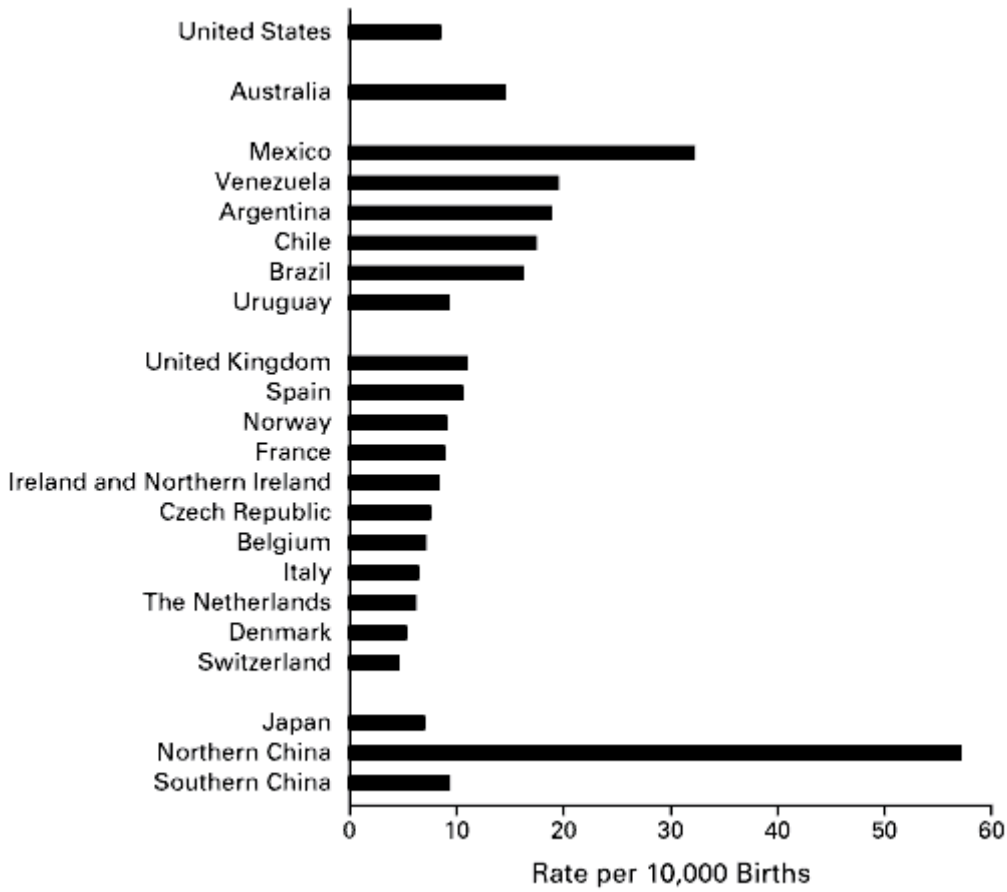

Fig. 1 International variation in the rates of spina bifida and anencephaly[1]

Etiology of NTD

Chromosomal abnormalities (trisomy 9, 13, 18 or triploidy), single gene mutations (e.g. Meckel-Gruber syndrome), maternal disease (diabetes or fever) or maternal exposure to teratogens (viral infections, radiation, hypo and hypervitaminosis A, alcohol, valproic acid, or other antiepileptic drugs) were implicated in 12% of cases [2,6]. These teratogens cause NTD by acting as folic acid antagonists, or by associating with inadequate folic acid availability to the embryo [2]. In most cases, the cause appears to be multifactorial (genetic-environmental interaction) [2,6]. Among parents who had a previous child with a NTD, the usual recurrence rate is 3-5% in subsequent pregnancies; however, about 90-95% of women who had a fetus or baby with a NTD had no previous history of offspring with NTD[2,7].

Genetics of NTD

Folic acid, which human can not synthesize themselves and can only receive from dietary sources, is involved in the synthesis of nucleic acids composing DNA, genes, and chromosomes; furthermore, folic acid is metabolized to tetrahydrofolic acid (THFA), which is one of three coenzymes (B6 and B12) that converts homocysteine to methionine [6] (Fig. 2).

Correspondence to: Pornswan Wasant MD, Professor of Pediatrics, Division of Medical Genetics, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Road, Bangkok, Thailand. Tel: 66-2-419-8414, 66-2-419-7000 extension 5944 Fax: 66-2-419-8414. E-mail: sipws@mahidol.ac.th

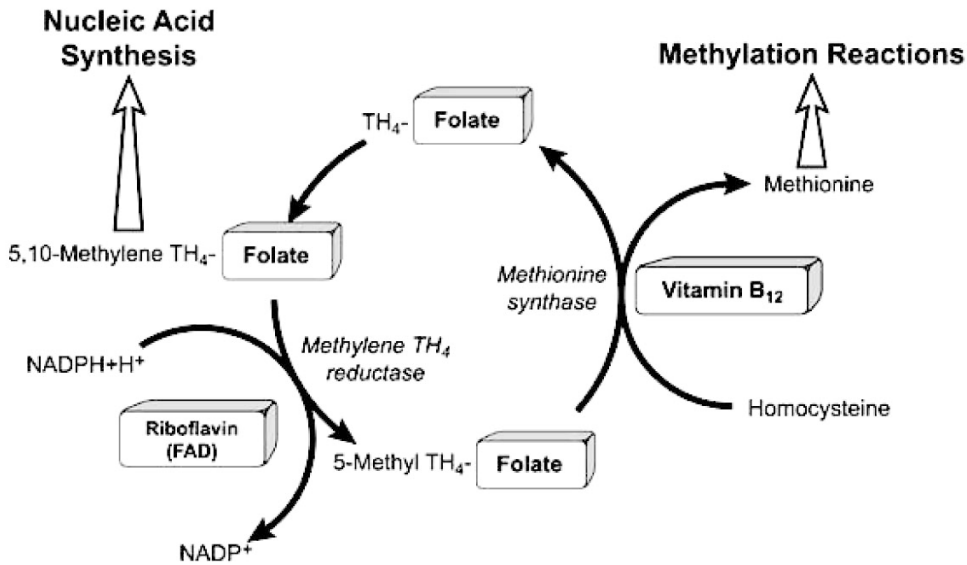

Fig. 2 Folic acid metabolism (http://lpi.oregonstate.edu/infocenter/vitamins/fa/fadiag1.html)

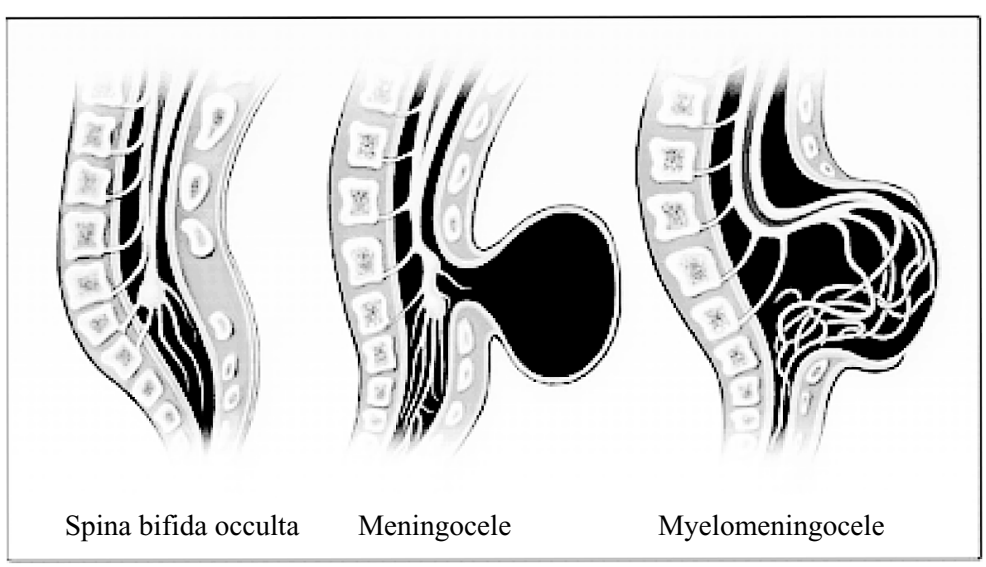

Fig. 3 lateral view of the spinal cord in three types of spina bifida[1]

If folic acid or THFA decreases, homocysteine will increase. Such increase is linked to an increase risk of atherosclerosis, venous thrombosis, osteoporosis, dementia, early pregnancy loss, pregnancies complicated by cleft lip and NTD [2,6]. Research in this field has led to numerous studies of different genes involved in the folate metabolic pathway, including the most commonly studied thermolabile mutation (C677T) in the MTHFR gene (methylenetetrahydrofolate reductase gene) [4-5]. A lack of folic acid, and mutation of MTHFR gene can explain elevated plasma homocysteine levels. In addition, it can explain up to 50% of the protective effect of folic acid against NTD[2].

Development of NTD

Spina bifida: a name characterized by incomplete fusion of the vertebral arches with a protruding sac containing meninges, spinal cord or nerve roots that cause permanent damage to the spinal cord and spinal nerves [2] (Fig. 3).

Anencephaly: a lethal malformation characterized by the absence of the cranial vault and the cerebral hemisphere that usually results in stillbirth or death within hours or days [2] (Fig. 5).

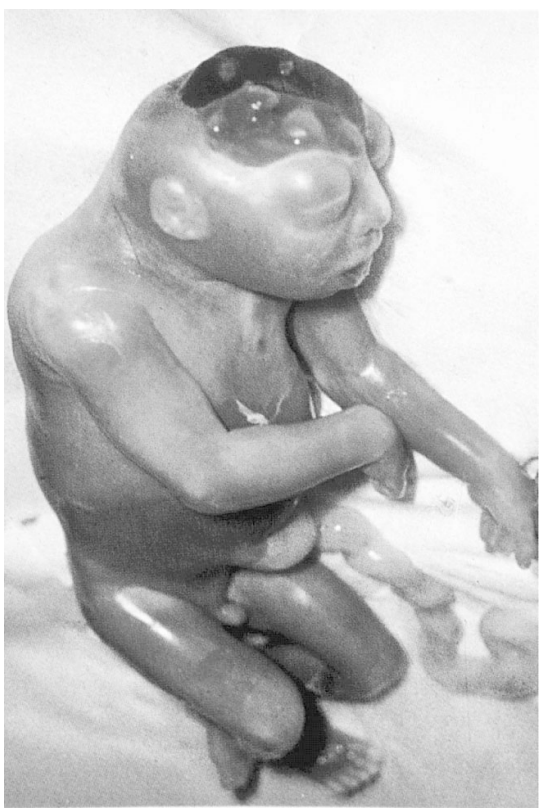

Fig. 5 Anencephaly

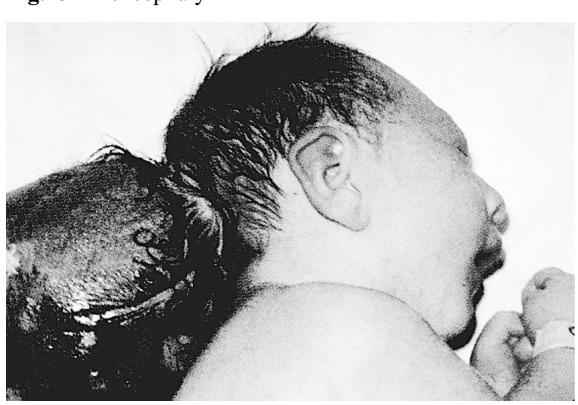

Fig. 6 Occipital encephalocele

Encephalocele: a congenital defect of the skull resulting in herniation of meninges and brain tissue, most commonly in the occipital region [2] (Fig. 6).

Two weeks after conception, the primitive nervous system begins as a flat neural plate which becomes indented by a longitudinal groove at 20 days, with neural folds on the flanks. These folds begin to fuse in the midline, forming a cylinder in the middle of the plate. In a zipper fashion, this dorsal closure is occurred rostally and caudally, resulting in a tubular structure with an open anterior and posterior aperture. The anterior aperture closes at 26 days followed by the posterior aperture at 29 days [2] (Figure 4). The development and closure of the neural tube are normally completed within 28 days after conception, before many women are aware that they are pregnant [1]. It is generally accepted that neural-tube defects are caused by the failure of the neural tube to close, although it has also been suggested that a closed tube may reopen in some cases[9].

Diagnosis of NTD

Alpha-fetoprotein (AFP), which is produced in the yolk sac early in gestation and later in the fetal liver and gut, exhibits maximal fetal plasma levels at 12-13 weeks of gestation. AFP is secreted in the amniotic fluid and passes into the maternal circulation, which can be measured in maternal blood during the first trimester[10]. Maternal serum screening for AFP is performed between 15 and 20 weeks of gestation, and level will increase in case of open NTD fetus. Of all congenital anomalies, NTD are among the easiest to identify prenatally by ultrasound screening[10]. The overall sonographic detection rate is approximately 80% for NTD, and the sensitivity of detection of anencephaly is almost 100%, but it is only 60% for spina bifida[10].

Folic acid for the prevention of NTD

Increasingly, new findings disclose the biochemistry, developmental biology and molecular genetics underlying neural-tube defects, and lead to make possible further strategies for prevention[1]. There is clear evidence that a large proportion of NTD is preventable by periconceptional folic acid intake[6-8]. The timing of folic acid supplementation is considered as significant factor to prevent NTD which is more effective when treatment is initiated at least 1 month prior to conception[6]. In September 1992, the United

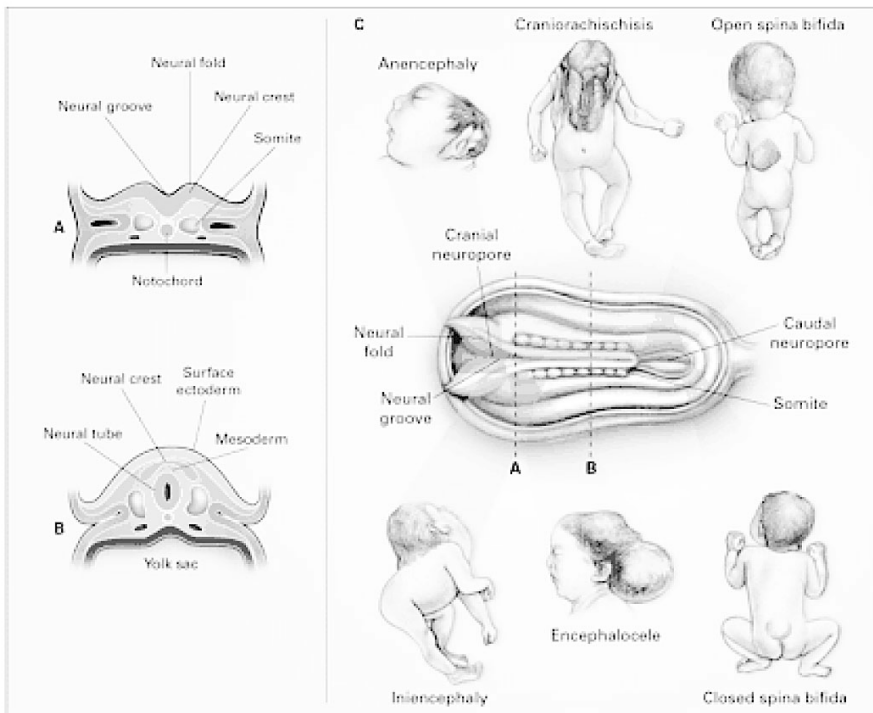

Fig. 4 features of neural-tube development and neural-tube defects [1]

States Public Health Service (USPHS) issued the recommendation that all women of child-bearing age who are capable of becoming pregnant need to consume 0.4 mg of folic acid daily, and for women who already have had an NTD-affected pregnancy should receive 4 mg of folic acid every day starting 1-3 months prior to the planned conception and continuing throughout the first 3 months of pregnancy [2,6,16].

Results

Incidence

Over 10 years of study(1990-1999), there were 115 patients treated in the Department of Pediatrics and other Departments at Siriraj Hospital. The total births during these 10 years were around 180,000; therefore, the incidence of NTD at Siriraj Hospital is 0.67 per 1,000 births.

Type of NTDs

Of the total NTD cases, 105 (91%) were isolated NTD, which were anencephaly 45 (39%), encephalocele 14 (12 %), and myelomeningocele 55 (48%). The cases of NTD with associated anomalies (8.7%) including 3 with cleft lip/palate, 1 with imperforated anus, 1 with amniotic band finger, 1 with ambiguous genitalia, 1 with laryngomalacia, and 3 with club feet.

Table 1. Types of NTD studied

Type	Number of cases
Anencephaly	45
Encephalocele	14
Myelomeningocele	55
Other	1
Total	115

Table 2. Associated anomalies of NTD studied

Other anomalies	Number of cases
Cleft lip/palate	3
Club feet	3
Laryngomalacia	1
Imperforated anus	1
Banding finger	1
Ambiguous genitalia	1
Total	10

Parental Age

Distribution of maternal and paternal ages was shown below.

Table 3. Distribution of parental age of NTD studied

Age (years)	Maternal age (No.of cases)	Paternal age (No.of cases)
16-20	12	2
21-25	15	20
26-30	32	22
31-35	20	18
36-40	5	12
> 40	5	4
No data	26	37
Total	115	115

Sex distribution

The sex distribution among NTD cases was equal (59 males, 55 females, 1 unknown). The details of age and sex of the patients first seen at Siriraj Hospital were shown below.

Table 4. Age and sex distributions of the patients

Age	Male	Female	Unknown
birth	28	24	1
1 day-1 yr	20	29	0
1-10 yr	8	10	0
10-20 yr	2	0	0
20-30 yr	0	1	0
30 -40 yr	1	1	0
Total	59	55	1

Treatment

Of all NTD cases studied, surgical corrections were performed in 95 cases: 47 excision and repair, 45 excision and VP shunt, 1 laminectomy, and 2 club feet correction.

Table 5. Treatment received in NTD studied

Treatment	No. of cases
Excision and repair	47
Excision, repair and VP shunt	45
Laminectomy	1
Correction of club feet	2
Total	95

Death

Of all NTD cases studied, 17 cases were dead, 7 cases dead fetus in utero, 8 cases early neonatal death, 2 cases death after 1 year.

Table 6. Death in NTD studied

Death	No. of cases
Dead fetus in utero	7
Early neonatal death	8
Late neonatal death	0
age > 1 year	2
Total	17

Discussion

Neural tube defects are a worldwide problem, affecting an estimated 300,000 or more fetuses or infants each year [1-3]. In the USA, the CDC recommendation for folic acid supplementation was made in 1992 [6]. In China, periconceptional use of daily supplements containing 400 ug of folic acid led to a 79% reduction in NTD risk in northern China and a 41% reduction in the southern China [11].

In Thailand, there is no study about the effect of folic acid supplementation in child-bearing women, but there was one previous study of NTD (unpublished data) which was a five-year study, 1983-1987, from Division of Medical Genetics, Department of Pediatrics, Siriraj Hospital. The incidence in that study was 0.6 per 1,000 births. In addition, there were other studies about birth prevalence and incidence of NTD or anencephaly from other hospitals [13-15]. However, associated anomalies, complications of treatment, parental age, and death of neural tube defects in Thailand are not well established. So, the objective of our study is to determine information of neural tube defects at Siriraj Hospital, which had 18,000-20,000 deliveries annually. The previous prevalence or incidence reports of NTD in Thailand from Srinagarind Hospital and Maharaj Nakorn Chiang Mai Hospital were 0.97 and 0.66 per 1,000 births respectively [14-15]. There was one study of anencephaly at Ramathibodi Hospital which the rate of anencephalic births was 0.62/1,000 [13]. Our study showed the incidence was 0.67 cases per 1,000. Since Siriraj hospital is the largest referral medical center in Thailand, there were large number of referrals to our hospital for further management.

The frequency of associated structural anomalies varies considerably from study to study, but overall averages are about 20% [1]. In our study, there were 10 cases (8.7%) with associated structural anomaly. The sex distribution ratio male:female is 1.07:1 which is similar to other studies. There were 40 cases underwent surgery and 17 cases were dead.

In general, patients who are born with myelomeningocele, not including anencephaly and encephalocele, will have 80% to 85% chance of developing hydrocephalus which requires cerebrospinal fluid shunt surgery [12]. In our study, 45 cases of all NTD (39%) were received VP shunt surgery.

At present, the incidence of NTD is declining throughout the world following prenatal screening by using ultrasonography and maternal serum AFP[2]. Moreover, widely use of periconceptional folic acid supplements in many countries has reduced the incidence of NTD [2]. In USA, there is folic acid supplement in cereals, and other fortified foods which the measure of which is important since synthetic folic acid is twice as absorbable as naturally occurring food folate[6,16]. Evidence to date suggests that supplementation with 0.4 mg of folic acid prevents the occurrence of >50% of NTD when it is taken before conception and continued throughout the first trimester of pregnancy[7,16].

References

1. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. N Engl J Med 1999;341: 1509-19.
2. Iqbal MM. Prevention of neural tube defects by periconceptional use of folic acid. Pediatr Rev 2000;21:58-66.
3. The Centers for Disease Control and Prevention (CDC). Preventing Neural Tube Birth Defects: A Prevention Model and Resource Guide. Atlanta: CDC, 1998.
4. George TM, Speer MC, the NTD Collaborative Group. Genetic and embryological approaches to studies of neural tube defects: A critical review. Neurol Res 2000;22:117-22.
5. Cunha ALA, Hirata MH, Kin CA, Guerra-Shinohara EM, Nonoyama K, Hirata RSC. Metabolic effects of C677T and A1298C mutations at the MTHFR gene in Brazilian children with neural tube defects. Clinica Chimica Acta 2002;318:139-43.
6. Hasenau SM, Covington C. Neural tube defects: prevention and folic acid. MCN Am J Matern Child Nurs 2002;27:87-91.
7. Committee on Genetics-American Academy of Pediatrics. Folic acid for the prevention of neural tube defects. Pediatrics 1999;104:325-7.
8. Stevenson RE, Allen WP, Pai GS, Best R, Seaver LH, Dean J, et al. Decline in prevalence of neural tube defects in a high-risk region of the United States. Pediatrics 2000;106:677-83.
9. Campbell LR, Sohal GS. The pattern of neural tube defects created by secondary reopening of the neural tube. J Child Neurol 1990;5:336-40.
10. Birnbacher R, Messerschmidt AM, Pollak AP. Diagnosis and prevention of neural tube defects. Curr Opin Urol 2002;12:461-4.
11. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 1999;341:1485-90.
12. Rintoul NE, Sutton LN, Hubbard AM, Cohen B, Melchionni J, Pasquariello PS, et al. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. Pediatrics 2002;109:409-13.
13. Suthutvoravut S, Chaturachinda K. Anencephaly at Ramathibodi Hospital. J Med Assoc Thai 1988;71(Suppl 2):16-20.
14. Ratanasiri T, Piensriwatchara E, Prasertcharoensuk W. Birth prevalence of neural tube defects at Srinagarind Hospital, 1988-1996. Srinagarind Med J 1997;12:139-43.
15. Kitisomprayoonkul N, Tongsong T. Neural tube defects: a different pattern in Northern Thai population. J Med Assoc Thai 2001;84:483-8.
16. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41:1-8.

การศึกษาภาวะหลอดประสาทไม่ปิดในโรงพยาบาลศิริราช 10 ปี (พ.ศ. 2533-2542)

พรสวรรค์ วสันต์, อัจฉรา เสถียรกิจการชัย

วัตถุประสงค์: *ภาวะหลอดประสาทไม่ปิด (anencephaly, meningocele, encephalocele) เป็นความพิการแต่กำเนิดที่พบบ่อยที่สุด ซึ่งมีความรุนแรงและมีอัตราการตายสูง อุบัติการณ์ 1-5 ต่อทารกคลอดมีชีพ 1,000 คน พบว่ามีความหลากหลายในเชื้อชาติและนานาประเทศ สำหรับประเทศไทยยังไม่มีการศึกษาอุบัติการณ์ ความพิการแต่กำเนิดที่เกิดร่วมภาวะแทรกซ้อนจากการรักษา และเศรษฐฐานะของครอบครัวผู้ป่วยที่มีภาวะหลอดประสาทไม่ปิด วัตถุประสงค์ของการศึกษานี้เพื่อทราบข้อมูลเกี่ยวกับภาวะหลอดประสาทไม่ปิดในโรงพยาบาลศิริราช ซึ่งมีอัตราการเกิด 18,000 - 20,000 ต่อปี*

วัสดุและวิธีการ: *การศึกษาโดยการทบทวนแฟ้มประวัติผู้ป่วย 115 ราย ที่เกิดที่โรงพยาบาลศิริราช หรือถูก ส่งตัวมารับการรักษาที่โรงพยาบาลศิริราชเป็นระยะเวลา 10 ปี (ระหว่าง พ.ศ. 2533-2542)*

ผลการศึกษา: *ในระหว่าง 10 ปี ที่ทำการศึกษาวิจัย พบผู้ป่วยทั้งหมด 115 ราย ที่มีภาวะหลอดประสาทไม่ปิด อุบัติการณ์เท่ากับ 0.67 ต่อ 1,000 พบได้ทั้งเพศชายและหญิงในสัดส่วนที่เท่ากัน (หญิง 55, ชาย 59 , ไม่ทราบเพศ 1) พบภาวะหลอดประสาทไม่ปิดอย่างเดียวร้อยละ 91 และร้อยละ 8.7 พบมีความพิการแต่กำเนิดอย่างอื่นร่วมด้วย เช่น ปากแหว่งเพดานโหว่ ไม่มีรูทวาร นิ้วที่ถูกตัดโดยพังผืดในถุงน้ำคร่ำ และอวัยวะเพศกำกวม พบ anencephaly ร้อยละ 39, encephalcele ร้อยละ 12, myelomeningocele ร้อยละ 48 ผู้ป่วย 17 รายเสียชีวิต โดยเสียชีวิตในครรภ์ 7 ราย เสียชีวิตในช่วงทารกแรกเกิด 8 ราย และเสียชีวิตภายใน 1 ปี 2 ราย*

สรุป: *การศึกษาวิจัยนี้ซึ่งเป็นลักษณะ hospital-based ในผู้ป่วยโรคหลอดประสาทไม่ปิดทั้งหมด 115 ราย พบอุบัติการณ์ 0.67 ต่อ 1,000 ของทารกแรกเกิดมามีชีพ อย่างไรก็ดีเนื่องจากเป็นการศึกษาวิจัยในโรงพยาบาล จึงยังไม่สามารถบอกอุบัติการณ์ที่แท้จริงในประชากรได้ ซึ่งน่าจะสูงกว่านี้ จากการศึกษาพบว่าส่วนใหญ่เป็น isolated NTDs อีกครึ่งหนึ่งพบเป็น meningomyelocele พบมีอัตราการตายสูง สมควรมีการศึกษาเพิ่มเติมเพื่อให้ข้อมูลเกี่ยวกับภาวะของโรคนี้ในประเทศไทยชัดเจนยิ่งขึ้น การแทรกแซงช่วยเหลือโดยให้กรดโฟลิคในช่วงก่อนปฏิสนธิ ควรได้รับการส่งเสริมและดำเนินการโดยกระทรวงสาธารณสุข เพื่อลดอุบัติการณ์ของหลอดประสาทไม่ปิดในประเทศไทยต่อไป*