Neural Tube Defects in Algeria

Bakhouche Houcher[1], Samia Begag[1], Yonca Egin[2] and Nejat Akar[2]
[1]Faculty of Sciences, Department of Biology University of Sétif, Sétif
[2]Department of Pediatric Molecular Genetics,
University Medical School, Ankara,
[1]Algeria
[2]Turkey

1. Introduction

Neural tube defects (NTD) are severe congenital malformations and can be fatal. These malformations constitute one of the principal causes of mortality and morbidity in childhood. Classically, NTD have been divided into two main groups: (a) defects affecting cranial structures, such as anencephaly and encephalocele, and (b) defects involving spinal structures (spina bifida) (Verrotti et al., 2006). In newer classification schemes for the NTD, encephalocele shows more similarities to spina bifida or anencephaly than it shows differences with respect to characteristics, temporal trend and the impact of fortification (Rowland et al., 2006).

In recent years, various clinical and experimental studies have demonstrated that folic acid supplementation during the periconceptional period can prevent the occurrence and recurrence of NTD (Czeizel and Dudas, 1992). Thus, a low folate status is associated with an increased NTD risk. Up to 70% of human NTD can be prevented by folate supplementation during the periconceptional period (Czeizel and Dudas, 1992; MRC Vitamin Study Research Group, 1991).

Both genetic and environmental factors such as the maternal vitamin status have been proposed to affect the risk for NTD (Copp et al., 1990). The incidence is nearly 1 in 1,000 births, but various numbers have been reported from different countries (Botto, 2000). At present, the exact mechanism through which folic acid works remains unknown (Morrison et al., 1998). It is known that folic acid plays an important role in the homocysteine metabolism, in which 5-methylene-tetrahydrofolate (THF), formed upon reduction of 5,10-methyl-THF by the enzyme methylene-THF reductase (MTHFR), donates its methyl group via the vitamin- B_{12}-dependent enzyme methionine synthase to homocysteine to form methionine. Another major pathway of homocysteine metabolism is the transsulfuration pathway, in which homocysteine is irreversibly condensed with serine to cystathionine by the vitamin B_6-dependent enzyme cystathionine β-synthase (Afman et al., 2003).

The genetic risk factors for NTDs have been intensively studied in recent years. As a result, numerous candidate genes associated with folate metabolism have been studied in detail and their association with NTD, including MTHFR (Selhub et al., 1993). The prevalence of

MTHFR C677T genotypes varies among different ethnic groups. It is low in Africa, whereas in Europe and North America it ranges between 5% and 15%, thereby suggesting regional differences in the MTHFR C677T distribution (Almawi et al., 2004). For example, a high prevalence of the TT genotype was reported for Mexico (34.8%) (Mutchinick et al., 1999), Italy (21.4%) (D'Angelo et al., 2000) and France (16.8%), while lower prevalences were reported for Thailand (1.4%) and India (2.0%).

There are several studies that have found a positive association between NTD and the common mutation C677T of MTHFR, and other studies that have not found such an association. Van der Put et al. (1995) discovered that a common genetic defect in the *MTHFR* gene, the C677T mutation, resulting in a reduced but not an abolished enzyme activity, is a genetic risk factor for spina bifida. The C677T mutation is associated with a 2- to 4-fold increased risk if an NTD mother is homozygous for this mutation.

Data from several association studies on different ethnic groups have resulted in conflicting conclusions about the role of the C677T mutation of the MTHFR gene, as a risk factor for NTD (Rampersaud et al., 2003).

In the present study, we aimed to determine the prevalence of the MTHFR C677T polymorphism in the Algerian population and evaluated their impact on NTD individuals and their relatives.

2. Patients and methods

2.1 Study population

The study was a retrospective review of the medical case notes over a 3-year period. Infants born with a NTD were identified from the University Maternity Hospital of Sétif (Algeria) database. The following items are routinely collected for each case: birth date, sex, single or multiple birth, presence of additional congenital malformations, mother's county of residence and birth date. The proportion of all congenital anomalies on the register accounted for by NTD was calculated. Prevalence (birth) rates per 1,000 births were examined each year for 3 year study period. The following factors were compared by type of NTD: prevalence, sex ratio, mother's age and season of birth. It was not possible to identify stillbirths with NTD born at home and we have no data on prenatal diagnosis of NTD by ultrasound among our patients.

2.2 Sample collection and DNA extraction

The total study group consisted of 71 mothers and 27 fathers. A group of 147 apparently healthy adult (82 women and 65 men) were used as control group. Peripheral blood samples were collected by venipuncture, collected in test tubes which contained EDTA as an anticoagulant and maintained frozen at -20°C until extraction of DNA and genotyping. The research protocol was approved by the Sétif Medical Faculty Ethics Committee.

DNA extraction was performed using the conventional phenol-chloroform method. After haemolysis of the blood in hypotonic solution, the DNA was isolated by using a simple proteinase K treatment at 65°C in the presence of SDS, followed by ammonium actetate precipitation of debris and ethanol precipitation of the DNA. Then, DNA amount and DNA

purity were quantified for each DNA sample by spectrophotometry (Nanodrop ND-1000). DNA samples were stored at -4°C until use.

2.3 Polymorphism analysis by LightCycler PCR® and melting curve analysis

The genetic analysis of the MTHFR C677T polymorphism was performed by real-time polymerase chain reaction (PCR) via a melting curve analysis performed on a Light Cycler (Roche Molecular Biochemicals, Mannheim, Germany) in borosilicate capillaries with an MTHFR C677T polymorphism detection kit (Roche Molecular Biochemicals). Primers and fluorescence-labelled hybridization probes designed were used. The primer sequences were: 5'-TGGCAGGTTACCCCAAAGG-3' (forward) and 5'-TGATGCCCATGTCGGTGC-3' (reverse) and hybridization probe sequences were:
 5'-TGAGGCTGACCTGAAGCACTTGAAGCACTTGAAGGAGAAGGTGTCT-3'-Flu and 5'-LC-640-CGG GAG CCG ATT TCA TCA T-3'-PHO (TIB Molbiol, Berlin Germany).

The 20.0 µl amplification reaction was prepared, containing 5.0 µl genomic DNA, 1.6 µl Mg, 4.0 µl Reagent Mix (Specific primers and probe, Tib molbion), 2 µl Fast Start DNA master HybProbe (Roche Diagnostics Mannheim, Germany), 7.4 µl H2O (PCR-grade).

Cycling conditions for MTHFR were initial denaturation at 95°C for 10 min, followed by 45 cycles with denaturation at 95°C for 5 s, annealing at 60°C for 10 s and extension at 72°C for 15 s. After amplification, melting curves have been generated following denaturation of the reaction at 95°C for 20s, holding the sample at 40°C for 20s and then slowly heating the sample to 85°C with a ramp rate of 0.2°C/s and simultaneous monitoring of fluorescence decline.

The identification of the *MTHFR* genotype has been performed by an analysis of the melting peaks of the run of the real-time PCR. The presence of just 1 melting peak at 63.0°C indicates a wild–type genotype, 2 melting peaks at 54.5°C and 63.0°C indicate a heterozygous mutant, and 1 melting peak at 54.5°C indicates a homozygous mutant (fig. 1).
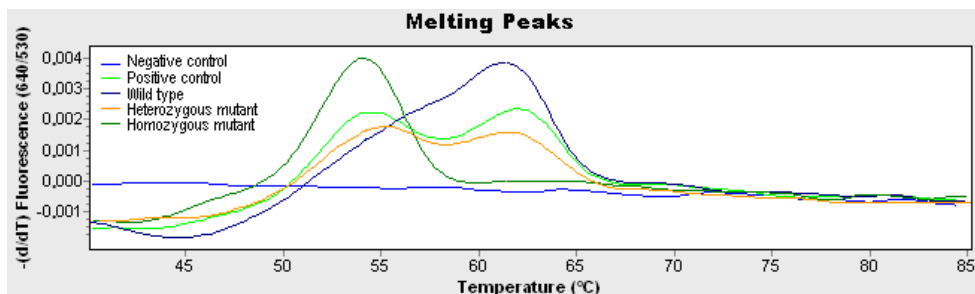

Fig. 1. Melting-curve analysis was performed analyze the MTHFR C677T polymorphism

2.4 Statistical analysis

Comparisons of NTD between sex and/or between mother's age and of genotype and allele frequencies between cases and control subjects were done by a χ^2 test. Allele frequencies were deduced from genotype distribution Statistical significance was accepted at $p < 0.05$. The odds

ratios (OR) as well as their 95% CI were computed to assess strength of association, if any, between different genotypes and NTD. We calculated the OR and associated 95% CI for individuals who were homozygous for the thermolabile variant at MTHFR (TT).

3. Results

The annual prevalence of all types of NTDs during the 3 years treated in the Service of Pediatrics and Genocology-Obstetrics at Sétif Hospital (Algeria), was 7.3, 8.2 and 7.1 NTD cases per 1000 live births and fetal deaths. The total NTDs numbered 215 and the total live births and fetal deaths were around 28,500. Therefore, the incidence of NTD at Sétif Hospital is 7.5 per 1,000 births.

Of the total NTD cases, there where 122 (56.7%) with spina bifida, 69 (32.1%) with anencephaly, 1 (0.5%) with encephalocele and 23 (10.7%) with spina bifida and anencephaly; the corresponding birth prevalence per 1000 births was 4.35 for spina bifida, 2.42 for anencephaly, 0.70 for spina bifida and anencephaly and 0.03 for encephalocoele.

Table 1. shows the characteristics of cohorts of the different types of NTD. The sex distribution among NTD cases was significantly different, 126 (58.6%) females, 88 (40.9%) males (p <0.05) and one (0.5%) unknown or indeterminate. There were also significant differences between the type of NTD with regard to the female to male sex ratio. The female sex ratio was significantly higher for anencephalics (1.76) and spina bifida and anecephalics (4.0) compared with spina bifida (1.1) (p <0.05). Of all NTD cases studied, hundred and seventeen (54.4%) cases died in utero and 4 cases (1.9%) unknown. The trend had not significantly changed for spina bifida and anencephaly during the 3 year period. The spina bifida/anencephaly ratio for the 3 year period was 1.77 (122/69).

Of the 215 NTD cases in the study, there were 64 (29.8%) with associated hydrocephalus anomalies. This study shows 13% (28/215) of the parents with affected newborns had consanguineous marriages. The rate of affected newborns was highest in mothers aged between 31-35 years (21.9%) (Tab. 1). Seasonal variation in the birth prevalence of NTD during the 3 year period was observed. Birth prevalence of NTD was higher in the January-June period (58.14%) compared with the July-December period (41.86%). The rate of NTD in May and June was 13.5 and 15.8% respectively, and was higher than for other months.

Variable	Type of defect				Total	χ^2	P-value
	Spina bifida	Anencephaly	Spina bifida +Anencephaly	Encephalocele			
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)		
Sex							
Male	59 (67.0)	25 (28.4)	4 (4.5)	0 (0.0)	88 (100)	5.02	0.05
Female	65 (51.6)	44 (34.9)	16 (12.7)	1 (0.8)	126 (100)		
Mother's age (y)							
20	4 (57.1)	1 (14.3)	2 (28.6)	0 (0.0)	7 (100)	14.28	0.01
21-25	24 (60.0)	11 (27.5)	5 (125)	0 (0.0)	40 (100)		
26-30	23 (67.6)	9 (22.5)	2 (59)	0 (0.0)	34 (100)		
31-35	20 (42.5)	22 (46.8)	5 (10.6)	0 (0.0)	47 (100)		
36	21 (56.7)	13 (35.1)	2 (5.4)	1 (2.7)	37 (100)		
Consanguinity	16 (57.1)	9 (32.1)	3 (10.7)	0 (0.0)	28 (100)		
Death	30 (25.6)	64 (54.7)	23 (19.6)	0 (0.0)	117 (100)		

Table 1. Characteristics of cohorts of the different types of NTD.

The observed frequencies of the various genotypes and alleles of C677T polymorphisms in the *MTHFR* gene are shown in Table 2. Forty-two (46%) out of 92 mothers analysed for the C677T polymorphism carried the T allele and 15 (16%) were homozygotes (table 2). Finally, 5 (10%) out of 48 fathers had the TT genotype and 22 (46%) were heterozygotes (Tab. 2). In the control mothers group (n = 82), 35 (43%) were heterozygotes (table 3). In the control mothers group (n = 82), 35 (43%) were heterozygotes and 14 (17%) were homozygotes (table 2). These frequencies were not significantly different from those observed in a sample of the general population (n = 147) (table 3).

There was no statistically significant difference between the genotype and allele frequencies of C677T polymorphisms in mothers with a previous child with NTD compared with mother controls. The allele frequencies for the MTHFR C677T polymorphism were similar in case mothers and control mothers, with approximate allele frequencies of 0.6 and 0.3 for C and T alleles, respectively (table 2). Comparisons of genotype frequencies between case mothers and controls did not reveal any statistically significant differences (tables 2, 3).

The frequency of C677T homozygotes in the couple was higher in mothers with a previous child with NTD than in corresponding controls (19 vs. 14%), but the difference was not statistically significant. The OR was 2.05 (95% CI: 0.78-5.41) (table 2). The frequency of T alleles too was higher in case mothers compared to controls (45 vs. 34%; OR = 1.55; 95% CI: 0.97-2.48), but the differences in frequencies were statistically insignificant (table 3).

	Control mothers (n = 82)	Case mothers (n = 92)	OR
CC	33 (0.40)	35 (0.38)	1
CT	35 (0.43)	42 (0.46)	1.13 (0.59-2.17)
TT	14 (0.17)	15 (0.16)	1.01 (0.42-2.41)
C	101 (0.62)	112 (0.61)	1
T	63 (0.38)	72 (0.39)	1.03 (0.67-1.59)

Table 2. Genotype and allele frequency of the MTHFR C677T polymorphism among control mothers and mothers with a previous child with NTD. Values in parentheses denote allele frequencies (columns 2 and 3) or 95% CI (column 4)

Variable	Controls (n = 147)	NTD mothers (n = 48)	NTD fathers (n = 48)	OR$_{NTD}$ mothers[1]	OR$_{NTD}$ fathers[1]
Genotype					
CC	67 (0.46)	14 (0.29)	21 (0.44)	1	1
CT	59 (0.40)	25 (0.52)	22 (0.46)	2.03 (0.97-4.26)	1.19 (0.6-2.38)
TT	21 (0.14)	9 (0.19)	5 (0.10)	2.05 (0.78-5.41)	0.76(0.26-2.26)
Allele C	193 (0.66)	53 (0.55)	64 (0.67)	1	1
Allele T	101 (0.34)	43 (0.45)	32 (0.33)	1.55 (0.97-2.48)	0.96 (0.59-1.56)

Values in parentheses denote allelic frequencies unless otherwise specified.
[1]OR (95% CI) versus controls.

Table 3. Genotype distribution and allelic frequency of the MTHFR C677T polymorphism among mothers and fathers of cases with a previous child with NTD and controls.

4. Discussion

Neural tube defects are a worldwide problem, affecting an estimated 300,000 or more fetus or infants each year (The Centers for Disease Control and prevention (CDC), 1998). The reported annual percentage fall in the rates of NTD was 3.1-7.7% for the United States and 10.6% for the United Kingdom (Windham & Edmands, 1982). Unfortunately we do not have previous data from our area or in all Algeria for comparison. This is the first report regarding NTD in Sétif (Algeria). Our study showed the incidence was 7.5 cases per 1,000. The trend over the 3 years remained fairly constant. Our rate is higher than studies in other countries such as Canada where it was 1.41/1,000 (DeWalls et al., 1992; Murphy, 1992; Van Allen et al., 1992; Wilson & Van Allen , 1993), in the United States of America 0.93 to 1.46/1,000 (Hendricks et al., 1999; Stevenson et al., 2000), in Germany 1.50/1,000 (Koch & Fuhrmann, 1984), in Holland 0.58/1,000 (Eurocat Working Group, 1991), in the North of England 1.79/1,000 (Rankin et al., 2000), in France 1,000 (Alembik et al., 1995; Candito & Van Obberghen, 2001), in Italy 0.36/1,000 (Eurocat Working Group, 1991), in South Africa 1.74/1,000 (Buccimazza et al., 1994), in Turkey 3.01/1,000 (Tuncbilek et al., 1999), in Jordan 1.63/1000 (Daoud et al., 1996), Palestine 5.49/1000 (Dudin, 1997), in United Arab Emirates 1.23/1000 (Samson, 2003), in Tunisia 2.2/1000 (Khrouf et al., 1986) and in Iran 2.87/1,000 (Golalipour et al., 2007). A higher prevalence in comparison with our results was observed in China 10.23-13.87/1000 (Dai et al., 2002; Li et al., 2006; Xiao et al., 1990) and Egypt 13.8/1000 (Samaha et al., 1995).

Spina bifida was the most common NTD in our study, which agrees with other studies (Golalipour et al., 2007; Harris & James, 1997; Soumaya et al., 2001; Wasant & Sathienkijkanchai, 2005), followed by anencephaly and encephalocele. The spina bifida to anencephalic ratio is similar to that reported by other workers (McDonnell et al., 1999). Our research was shown that more than half of mortality is a consequence of anencephaly (Eurocat Working Group, 1991).

In our study, there were 64 spina bifida (29.8%) with associated hydrocephalus anomalies. The etiology of congenital hydrocephalus is extremely heterogeneous and for instance it may be secondary to an open neural tube defect (Williamson et al., 1984). In general, patients with spina bifida, not including anencephaly and encephalocele, will have 80 to 85% chance of developing hydrocephallus (Rintoul et al., 2002). Also, it has been suggested that there is an increased risk for hydrocephalus in families with a propositus affected with NTD (Cohen et al., 1979).

As reported in many other studies (Lary & Paulozzi, 2001; Rittler et al., 2004), we also observed a significant females predominance. Regarding sex differences, our results indicate that the rate of NTD was higher in females than males (male to female ratio = 0.70). Others had reported 0.73 (Daoud et al., 1996), 0.78 (Golalipour et al., 2007; Stevenson et al., 2000) and 0.85 (Samson, 2003), or even a male predominance 1.07 (Wasant & Sathienkijkanchai, 2005). The predominance of female anencephalic births over males in our study is similar to that seen in other countries and likewise the slight female predominance in spina bifida births (McDonnell et al., 1999).

Our research showed that the highest rate of affected newborns was in mothers aged 31-35 years (21.9%), with 3.2% in mothers aged 16-20 years and 9.76% aged 36-40 years. Our

observation is different from other studies which show a linear relation between the rate of NTD and increasing maternal age (Golalipour et al., 2007) or which show, a U-shaped curve with a higher risk among younger mothers and higher rates in mothers aged over 35 years (Hendricks et al., 1999; Li et al., 2006). It may be due to factors such as lower rate of marriage under 20 years (sometimes even more than 25 years of age) and can be attributed to the use of contraceptive drugs using over 35 years.

In this study a seasonal variation in the birth prevalence of NTD was observed, it was higher in the January-June period compared with July-December period, then is similar to that reported by Mc Donnell et al. (1999). Some research has shown a predominance of NTD births in winter months particularly in October to December and January to March (Golalipour et al., 2007; Office for Population Censuses and Surveys, 1998). Our research has shown that rate of NTD was higher in May with a peak in June. In Ireland the peak prevalence was in April (McDonnell et al., 1999) and in Northern Iran it was in December (Golalipour et al., 2007). The seasonal variations in the birth prevalence and the peak of NTD observed in our population were difficult to compare with those of previous studies, which were performed in countries where income, seasonal changes in diet is completely different. The high prevalence of NTD it may be attributed to the low dietary intake of folate in our women population (Houcher et al., 2003) and related with the seasonal variation of folate consumption. For example, the folate dietary intake of Havanan men was lowest in June and July, which contrasts with improvement in folate intake in June and July observed in Gambian women (Bates et al., 1994), and with the increase in serum folate concentration during the summer observed in British men (Clarke et al., 1998).

It has shown that the rate of consanguineous marriage is high in NTD births (Murshid, 2000). In different Middle Eastern countries the rate of consanguineous marriages varies from 23.3% to 57.9% (Khoury & Massad, 1992; Teebi, 1994) The incidence of consanguineous marriage in Algeria was 23-34% (Benallegue & Kedji 1984; Zaoui & Biemont, 2002) and the frequency of consanguineous marriage rates were 40.5 and 30.6% in rural and urban settings, respectively (Zaoui & Biemont, 2002). First-cousin marriages constitute almost one-third of all marriages in many Arab countries (Hamamy et al., 2005). First-cousin marriage in Algeria was 10-16% (Zaoui & Biemont, 2002). In our study 13% of parents with affected newborns had consanguineous marriage (first-cousin). In families with children born with neural tube defects, the consanguinity rate was much higher than observed in the general population (Jaber et al., 2004; Khrouf et al., 1986; Zlotogora, 1997). The relatively high proportion of first cousin marriages among parents of individuals with neural tube defects suggests that some of these cases are due to monogenic disorders (Zlotogora, 1997). We were not able to confirm the suggestion that there is an increase risk for NTD in children born of consanguineous parents. The possibility that consanguinity could be a risk factor for NTD in a population requires further research (Murshid, 2000; Rajab et al., 1998).

Numerous articles have been published regarding the effect of folic acid intake on the reduction or prevention of NTD (Frey & Hauser, 2003; Li et al., 2006; Morin et al., 2001; Smithells et al., 1980; Stevenson et al., 2000). Intake of 0.4 mg per day of folic acid in the periconceptional period reduces the risk of NTD by 30-100% (Berry et al., 1999; Czeizel and Dudas, 1992; MRC Vitamin Study Research Group, 1991; Ray et al., 2002). Several studies have suggested that low vitamin B12 levels may be associated with an increased risk for

NTD (Candito et al., 2004; Kirke et al., 2004; Williams et al., 2005). Our NTD group showed a higher risk of NTD among our women population, which may in part be attributable to a lower daily folate intake of women in our previous report; it revealed a large proportion of women (69%) presenting with less than the Reference Nutrient Intake (RNI) for folate (Houcher et al., 2003). Possibly, the most important finding from this study was the very low periconceptional use of folic acid-containing vitamins among our women population. Only 2.4% women in our population consumed multivitamins daily (Houcher et al., 2003).

NTD is recognized to have a complex etiology, involving both environmental and genetic factors. The *MTHFR* gene is chosen for study because of its direct catalytic interaction with homocysteine, cobalamin and folate, which predicted risk factors in NTD (Kirke et al., 1993; van der Put et al., 1997). It has been shown that homozygosity for the common C677T mutation in the *MTHFR* gene is a genetic risk factor for NTD in man (van der Put et al., 1995; Ou et al., 1995).

The association between the C677T variant in the *MTHFR* gene and NTD is controversial in several populations worldwide. Our research is the first in Algeria, which studied NTD patients in order to determine the association of the T allele with NTD in the region of Sétif, where NTD are highly prevalent (Houcher et al., 2008). The MTHFR C677T gene polymorphism was neutral in our population. We found the same prevalence of the 677T *MTHFR* allele in mothers as in controls and in the general population. Our results on Algerian NTD mothers did not show a significant association for any group, suggesting that the thermolabile variant C677T in the MTHFR gene is not a risk factor for NTD for a mother to have NTD offspring. These data are not in agreement with those of others (Grandone et al., 2006), who reported a higher prevalence in mothers than in controls and in the general population. However, no association was found for mothers of offspring with NTD in Italy or in Ireland, two countries with a higher 677 T allele frequency (De Marco et al., 2002; Kirke et 2004).

Thus, homozygosity for *MTHFR 677T* may only be a risk factor for NTD in some ethnic groups and not in others (Papapetrou et al., 1996). The divergence between populations raises the question whether dietary factors could play a significant interactive role in C677T mutations. There is evidence that the risk for NTD in association with the *MTHFR* genotypes might vary depending on the nutritional status (Gonzalez-Herrera et al., 2002) and, especially, due to low levels of red cell folate (Martinez de Villarreal et al., 2001). It is also relevant to note that the incidence of the C677T variant differs markedly amongst populations. These differences do not correlate with the incidence of NTD; for example, the frequency of homozygosity for the 677T allele is 8.3% in Ireland where the prevalence of NTD is high, and 16% in Italy where the NTD prevalence is low (Morrison et al., 1998).

Davalos et al (2000), who included among their cases the mothers and fathers of children affected by NTD, also found no differences between the cases and the control groups concerning the maternal genotype or allelic frequencies. We found that mothers who are homozygous for the C677T mutation, have a 4-fold higher risk of having a child with an NTD. Thus, the *MTHFR* genotype of the father also contributes to the risk of NTD (Blom, 1998)

The thermolabile MTHFR C677T variant is a risk factor for NTD in some but not all populations (Botto and Yang, 2000) and is associated with low folate and elevated

homocysteine levels. The high prevalence of the *MTHFR 677T* allele (17%) (Bourouba et al., 2009), the higher risk of NTD (7.5 per 1,000 births) (Houcher et al., 2008) and lower daily folate intake (69%) of less than the reference nutrient intake for folate (Houcher et al., 2003), i.e. a combination of genetic and nutritional factors, may therefore play a role in the NTD rate in this region of Algeria, although the mechanism, by which the genotype or folate status increases the risk of NTD is not clear.

Our results support the hypothesis by Shields et al. (1999), which upholds that the 677T allele may only be a risk factor in populations with a poor folate diet, which could explain the lack of consistency among studies. Molloy et al. (1997) observed a decreased red cell folate in individuals that were homozygous for the C677T mutation. Consequently, the MTHFR A1298C variant was found to increase the risk of spina bifida when combined with MTHFR C677T alteration (Akar et al., 2000). However, it cannot be excluded that mutations of folate receptor genes correlate with NTD (De Marco et al., 2000) and can be involved in NTD etiology (Heil et al, 1999).

Currently, the molecular analysis in case of NTD is based on the examination of mutation (polymorphism) in genes, which is why it is difficult to determine their genetic basis. It seems that NTD diagnosis will be based on single nucleotide polymorphism analysis (Gos and Szpecht-Potocka, 2002). It has been established that the dihydrofolate reductase (DHFR) 19-bp intron deletion allele has a significant protective association by reducing the risk of woman having NTD of offspring in the Irish population (Parle-McDermott et al., 2007). Very recently, it has been reported that NTD mothers homozygous for the 19-bp del allele have a 2.04-fold greater risk compared to the controls in the Turkish population (Akar et al., 2008). In addition, Au et al. (2008) also found that several genes for glucose transport and metabolism are potential risk factors for meningomyolocele.

Several studies even pointed out that a folate intake high enough to prevent NTD cannot be achieved by a diet of folate–rich nutrition. Only intake of folate supplements or fortified foods such as flour and cereals can achieve these recommended daily values (van der Put et al., 1998). In terms of public health, we think that the most important finding from this study is the very low periconceptional use of folic-acid–containing vitamins among our population of women.

5. Conclusion

According to our findings genetic factors, interfamilial marriage and nutritional factors as folate deficiency may play a role in the NTD rate in this region of Algeria, although the mechanism, by which the genotype or folate status increases the risk of NTD, is not clear. So further investigations are needed, and we recommend that a central registry be set up to record NTD occurring in the Sétif region.

Several studies even pointed out that a folate intake high enough to prevent NTD cannot be achieved by a diet of folate–rich nutrition. Only intake of folate supplements or fortified foods such as flour and cereals can achieve these recommended daily values. In terms of public health, we think that the most important finding from this study is the very low periconceptional use of folic-acid–containing vitamins among our population of women.

6. Acknowledgment

7. References

Afman, LA. ; Lievers, KJA. ; Kluijtmans, LAJ. ; Trijbels, FJM. & Blom, HJ. (2003). Gene-gene interaction between the cystathionine β-synthase 31 base pair variable number of tandem repeats and the methylenetetrahydrofolate reductase 677C>T polymorphism on homocysteine levels and risk for neural tube defects. *Mol Gent Metab*, Vol.78, pp. 211-215, ISSN 1096-7192

Akar, N.; Akar, E.; Deda, G. & Arsan, S. (2000). Spina bifida and common mutations at the homocysteine metabolism pathway. *Clin Genet*, Vol.57, pp. 230-231, ISSN 0009-9163

Akar, N.; Akar, E.; Eğin, Y.; Deda, G.; Arsan, S. & Ekim, M. (2008). Neural tube defects and 19 bp deletion within intron-1 of dihydrofolate reductase gene. *Turk J Med Sci*, Vol.38, pp. 383-386, ISSN 1300-0144

Alembik, Y.; Dott, B.; Roth, MP. & Stoll, C. (1995). Prevalence of neural tube defects in northeastern France, 1979-1992 impact of prenatal diagnosis. *Ann Genet*, Vol.38, pp. 49-53, ISNN 0003-3995

Almawi, WY.; Finan, RR.; Tamim, H.; Daccache, JL. & Irani-Hakime, N. (2004). Differences in the frequency of the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene among the Lebanese population. *Am J Hematol*, Vol.76, pp. 85-87, ISSN 0361-8609

Au, KS.; Tran, PX.; Tsai, CC.; O'Byrne, MR.; Lin, J-I.; Morrison, AC.; Hampson, AW.; Cirino, P.; Fletcher, JM.; Ostermaier, KK.; Tyerman, GH.; Doebel, S. & Northrup, H. (2008). Characteristics of a spina bifida population including north American Caucasian and Hispanic individuals. *Birth Defects Research A* , Vol.82, pp. 692-700, ISNN 1542-0752

Bates, CJ.; Prentice, AM.; & Paul, AA. (1994). Seasonal variations in vitamins A, C, riboflavin and folate intake and status of pregnant and lactating women in a rural Gambian community: some possible implications. *Eur J Clin Nutr*, Vol.48, pp. 660-668, ISSN 0954-3007

Benallegue, A. & Kedji, F. (1984). Consanguinité et santé publique: Une étude algérienne. *Arch Fr Pédiatr*, Vol.41, pp. 435-40, ISSN 0003-9764

Berry, RJ.; Li, Z.; Erickson, JD.; Li, S.; Moore, CA.; Wang, H.; Mulinare, J.; Zhao, P.; Wong, LY.; Gindler, J.; Hong, SX. & Correa, A. (1999). Prevention of neural tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med*, Vol.341, pp. 1485-1490, ISNN 0028-4793

Blom, HJ. (1998). Mutated 5,10-methylenetetrahydrofolatereductase and moderate hyperhomocysteinemia. *Eur J Pediatr*, Vol.157, pp. S131-S134, ISSN 0340-6199

Botto, LD. & Yang, Q. (2000). 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGe review. *Am J Epidemiol*, Vol.151, pp. 862-877, ISSN 0002-9262

Bourouba, R., Houcher, B., Djabi, F., Egin, Y. & Akar, N. (2009). The prevalence of methylenetetrahydrofolate reductase 677 C-T, factor V 1691 G-A, and prothrombin

20210 G-A mutations in healthy populations in Sétif, Algeria. *Clin Appl Thromb Hemost*, Vol.15, pp. 529-534, ISNN 1076-0296

Buccimazza, S. ; Molteno, C. ; Dunne, T. & Viljoen, DL. (1994). Prevalence of neural tube defects in Cape Town, South Africa. *Teratology*, Vol.50, pp. 194-199, ISNN 0040-3709

Candito, M.; Houcher, B.; Boisson, C.; Abbellard, A.; Demarcq, MJ.; Gueant, JL.; Benhacine, K.; Gérard, P. & Van Obberghen, E. (2004). Neural tube defects and vitamin B12 : a report of three cases. *Ann Biol Clin (Paris)*, Vol.62, pp. 235-238, ISSN 0003-3898

Candito, M. & , Van Obberghen E. (2001). Folates, vitamine B12, homocystéine et anomalies du tube neural. *Ann Biol Clin (Paris)*, Vol.59, pp. 111-112, ISSN 0003-3898

Clarke, R.; Woodhouse, P.; Ulvik, A.; Frost, C.; Sherliker, P.; Refsum, H.; Ueland, PM. & Khaw, KT. (1998). Variability and determinants of total homocysteine concentrations in plasma in an elderly population. *Clin Chem*, Vol.44, pp. 102-107, ISSN 1530-8561

Cohen, T.; Stern, E. & Rosenman, A. (1979). Sub risk of neural tube defect. Is prenatal diagnosis indicated in pregnancies following the birth of a hydrocephalic child? *J Med Genet*, Vol.16, pp. 14-16, ISNN0022-2593

Copp, AJ.; Brook, FA.; Estibeiro, JP.; Shum, AS. & Cockroft DL. (1990). The embryonic development of mammalian neural tube defects. *Progr Neurobiol*, Vol.35, pp. 363-403, ISNN 0301-0082

Czeizel, AE. & Dudas, I. (1992). Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med*, Vol.327, pp. 1832-1835, ISSN 0028-4793

Dai, L.; Zhu, J.; Zhou, G.; Wang, Y.; Wu, J.; Miao, L. & Liang, J. (2002). Dynamic monitoring of neural tube defects in China during 1996 to 2000. *Chinese J Prevent Med*, Vol.36, pp. 402-405, ISNN 0253-9624

D'Angelo, A. ; Coppola, A. ; Madonna, P. ; Fermo, L., Pagano, A. ; Mazzola, G. ; Galli, L. & Cerbone, AM. (2000). The role of vitamin B12 in fasting hyperhomocysteinemia and its interaction with the homozygous C677T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene. A case-control study of patients with early-onset thrombotic events. *Thromb Haemost*, Vol.83, pp. 563-70, ISSN 0340-6245

Daoud, AS.; Al-Kaysi, F.; El-Shanti, H.; Batieha, A.; Obeidat, A. & Al-Sheyyab, M. (1996). Neural tube defects in Northern Jordan. *Saud Med J*, Vol.17, pp. 78-81, ISSN 0379-5284

Davalos, IP.; Olivares, N.; Castillo, MT.; Cantu, JM.; Ibarra, B.; Sandoval, L.; Moran, MC.; Gallegos, MP., Chakraborty, R. & Rivas F. (2000). The C677T polymorphism of the methylenetetrahydrofolate reductase gene in Mexican mestizo neural tube defect parents, control mestizo and native populations. *Ann Genet*, Vol.43, pp. 89-92, ISSN 0003-3995

De Marco, P.; Calevo, MG.; Moroni, A.; Arata, L.; Merello, E.; Finnell, RH.; Zhu, H.; Andreussi, L.; Cama, A. & Capra, V. (2002). Study of MTHFR and MS polymorphisms as risk factors for NTD in the Italian population. *J Hum Genet*,Vol.47, pp. 319-324, ISSN 0002-9297

DeWalls, P.; Trochet, C. & Pinsonneaut, L. (1992). Prevalence of neural tube defect in the province of Quebec. *Can J Pub Health*, Vol.90, pp. 237-239, ISSN 0008-4263

Dudin, A. (1997). Neural tube defects in Palestinians: a hospital based study. *Ann Trop Pediatr*, Vol.17, pp. 217-22, ISSN 0272-4936

Eurocat Working Group. (1991). Prevalence of neural tube defects in 20 regions of Europe and the impact of prenatal diagnosis 1980- 86. *J Epidemiol Community Health*, Vol.45, pp. 52-8, ISNN 0143-005X

Frey, L. & Hauser, WA. (2003). Epidemiology of neural tube defects. *Epilepsia*, Vol.44, pp. 4-13, ISNN 0013-9580.

Golalipour, MJ.; Mobasheri, E.; Vakili, MA. ; & Keshtkar, AA. (2007). Epidemiology of neural tube defects in Northern Iran, 1998-2003. *Eastern Mediterr Health J*, Vol.3, pp. 560-566, ISSN 1020-3397

Gonzalez-Herrera, L.; Garcia-Escalante, G. & Castillo-Zapata, I. (2002). Frequency of the thermolable variant C677T in the MTHFR gene and lack of association with neural tube defects in the State of the Yucatan, Mexico. *Clin Genet*, Vol.62, pp. 394-398, ISSN 0009-9163

Gos, M. & Szpecht-Potocka, A. (2002). Genetic basis of neural tube defects. II. Genes correlated with folate and methionine metabolism. *J Appl Genet*, Vol.43, pp.511-524, ISSN 1234-1983

Grandone, E.; Corrao, AM.; Colaizzo, D.; Vecchione, G.; Girgenti, CD.; Paladini, D.; Sardella, L.; Pellegrino, M.; Zelante, L.; Martinelli, P. & Margaglione, M. (2006). Homocysteine metabolism in families from southern Italy with neural tube defects: role of genetic and nutritional determinants. *Prenat Diagn*, Vol.26, pp.1-5, ISSN 0197-3851

Hamamy, H.; Jamhawi, L.; Al-Darawsheh, J.; & Ajlouni, K. (2005). Consanguineous marriages in Jordan: Why is the rate changing with time? *Clin Genet*, Vol.67, pp. 511-516, ISSN 0009-9163

Harris, JA. & James, L. (1997). State-by-state cost of birth defects-1992. *Teratology*, Vol.56, pp. 11-16, ISSN 0040-3709

Heil, SG.; van der Put, NMJ.; Trijbels, FJ.; Gabreels, FJ. & Blom, HJ. (1999). Molecular genetic analysis of human folate receptors in neural tube defects. *Eur J Hum Genet*, Vol.7, pp. 393-396, ISSN 1018-4813

Hendricks, KA.; Nuno, OM.; Suarez, L.; & Larsen R. (2001). Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. *Epidemiology*, Vol.12, pp. 630-635, ISSN 1044-3983

Hendricks, KA.; Simpson, JS. & Larsen, RD. (1999) Neural tube defect along the texas-Mexico border, 1993-1995. *Am J Epidemiol*, Vol.149, pp. 1119-27, ISSN 0002-9262

Houcher, B.; Bourouba, R.; Djabi, F. & Houcher, Z. (2008). The prevalence of neural tube defects in Setif university maternity hospital, Algeria-3 years review (2004-2006). *Pteridines*, Vol.19, pp. 12-18, ISSN 0933-4807

Houcher, B.; Potier de Courcy, G.; Candito, M.; van Obberghen, E. & Naimi, D. (2003). Nutritional assessment of folate status in a population of Setif, Algeria. *Pteridines*, Vol.14, pp. 138-142, ISSN 0933-4807

Jaber, L.; Karim, IA.; Jawdat, AM.; Fausi, M. & Merlob, P. (2004). Awareness of folic acid for prevention of neural tube defects in a community with high prevalence of consanguineous marriages. *Ann Genet*, Vol.47, pp. 69-75, ISSN 0003-3995

Khoury, SA. & Massad, D. (1992). Consanguineous marriage in Jordan. *Am J Med Genet*, Vol.43, pp. 769-775, ISSN 1552-4825

Khrouf, N. ; Spang, R. ; Podgorna, T. ; Miled, SB.; Moussaoui, M.; & Chibani, M. (1986). Malformations in 10,000 consecutive births in Tunis. *Acta Paediatr Scand*, Vol.75, pp. 534-539, ISNN 0001-656X

Kirke, PN.; Mills, J.; Molloy, AM.; Brody, LC.; O'Leary, VB.; Daly, L.; Murray, S.; Conley, M.; Mayne, PD.; Smith, O. & Scott, JM. (2004). Impact of the MTHFR C677T polymorphism on the risk of neural tube defect case-control study. *BMJ*, Vol.328, pp. 1535-1536, ISSN 0959-8146

Kirke, PN.; Molloy, AM.; Daly, LE.; Burke, H.; Weir, DG. & Scott, JM. (1993). Maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects. *Q J Med*, Vol.86, pp. 703-708, ISSN 1460-2725

Koch, M. & Fuhrmann, W. (1984). Epidemiology of neural tube defects in Germany. *Hum Genet*, Vol.68, pp. 97-103, ISSN 0340-6717

Lary, JM. & Paulozzi, LJ. (2001). Sex differences in the prevalence of human birth defects: a population-based study. *Teratology*, Vol.64, pp. 237-51, ISSN 0040-3709

Li, Z. ; Ren, A. ; Zhang, L. ; Ye, R.; Li, S.; Zheng, J.; Hong, S.; Wang, T. & Li, Z. (2006). Extremely high prevalence of neural tube defects in a 4-county area in Shanxi province, China. *Birth Defects Res A Clin Mol Teratol*, Vol.76, pp. 237-240, ISSN 1542-0752

Martinez de Villarreal, L.; Delgado-Enciso, I. ; Valdez-Leal, R. ; Ortiz-Lopez, R. ; Rojas-Martinez, A. ; Limon-Benavides, C. ; Sanchez-Pena, MA. ; Ancer-Rodriguez, J. ; Barrera-Saldana, HA. & Villarreal–Perez, JZl. (2001). Folate levels and N^5,N^{10}-Methylenetetrahydrofolate reductase genotype (MTHFR) in mothers of offspring with neural tube defects: a case-control study. *Arch medical Res*, Vol.32, pp. 277-282, ISSN 0188-4409

McDonnell, RJ.; Johnson, Z.; Delaney, V.; & Dack P. (1999). East Ireland 1980-1994: epidemiology of neural tube defects. *J Epidemiol Community Health*, Vol.53, pp. 782-8, ISSN 0143-005X

Molloy, A.; Daly, S.; Mills, J.; Kirke, PN.; Whitehead, AS.; Ramsbottom, D.; Conley, MR.; Weir, DG. & Scott, JM. (1997). Thermolabile variant of 5,10-methylenetetrahydrofolate reductase associated with low red-cell folates: implications for folate intake recommendations. *Lancet*, Vol.349, pp. 1591-1593, ISSN 0140-6736

Morin, VI.; Mondor, M. & Willson, RD. (2001). Knowledge on periconceptional use of folic acid in women of Brithsh Columbia. *Fetal Diagn. Ther*, Vol.16, pp. 111-115, ISNN 1015-3837

Morrison, K.; Papapetrou, C.; Hol, FA.; Mariman, ECM.; Lynch, SA.; Burn, J. & Edwards, YH. (1998). Susceptibility to spina bifida; an association study of five candidate genes. *Ann Hum Genet*, Vol.62, pp. 379-396, ISSN 0003-4800

MRC Vitamin Study Research Group. (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*, Vol.338, pp. 131-137, ISSN 0140-6736

Murphy, PA. (1992). Periconceptional supplementation with folic acid: does it prevent neural defects? *J Nurse-Midwifery*, Vol.37, pp. 25-32, ISSN 0091-2182

Murshid, WR. (2000). Spina bifida in Saudi Arabia : is consanguinity among the parents a risk factor ? *Pediatric neurosurgery*, Vol.32, pp.10-12, ISSN1016-2291

Mutchinick, OM. ; Lopez, MA. ; Luna, L. ; Maxman, J. & Babinsky, VE. (1999). High prevalence of the thermolabile methylenetetrahydrofolate reductase variant in Mexico: a country with a very high prevalence of neural tube defects. *Mol Genet Metab*, Vol.68, pp. 461-467, ISSN 1096-7192

Office for Population Censuses and Surveys. (1988). Congenital malformation statistics: notifications 1981-85. London: HMSO, ISBN 0116912251

Ou, CY.; Stevenson, RE.; Brown, VK.; Schwartz, CE.; Allen, WP.; Khoury; MJ., Rozen, R. & Oakley, GP. Jr. (1995). C677T homozygosity associated with thermolabile 5,10-methylenetetrahydrofolate reductase as a risk factor for neural tube defects. *Am J Hum Genet*, Vol.57, pp. 223, ISSN 0002-9297

Papapetrou, C.; Lynch, SA.; Burn, J. & Edwards, YH. (1996). Methylenetetrahydrofolate reductase and neural tube defects. Lancet, Vol.348, pp. 58, ISSN 0140-6736

Parle-McDermott, A.; Pangilinan, F.; Mills, JL.; Kirke PN.; Gibney, ER.; Troendle, J.; O'Leary, VB.; Molloy, AM.; Conley, M.; Scott, JM. & Brody, LC. (2007). The 19-bp deletion polymorphism in intron-1 of dihydrofolate reductase (DHFR) may decrease rather than increase risk for spina bifida in the Irish population. *Am J Med Genet A*, Vol.143, pp. 1174-1180, ISSN 1552-4825

Rajab, A. ; Vaishnav, A. ; Freeman, NV. & Patton, MA. (1998). Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. *J Trop Pediatr*, Vol.44, pp. 300-303, ISSN 0142-6338

Rampersaud, E.; Melvin, EC.; Siegel, D.; Mehltretter, I.; Dickerson, ME.; George, TM.; Enterline, D.; Nye, JS.& Speer, MC. (2003). Updated investigations of the role of methylenetetrahydrofolate reductase in human neural tube defects. NTD Collaborative group. *Clin Genet*, Vol.63, pp. 210-214, ISNN 0009-9163

Rankin, J.; Glinianaia, S. & Brown, R. (2000). The changing prevalence of neural tube defects: a population-based study in the north of England, 1984-96. Northern Congenital Abnormality Survey Steering Group. *Peadiatr Perinat Epidemiol*, Vol.14, pp. 104-110, ISSN 0269-5022

Ray, JG. ; Meier, C. ; Vermeulen, MJ. ; Boss, S.; Wyatt, PR.; & Cole, DE. (2002). Association of neural tube defects and folic acid food fortification in Canada. *Lancet*, Vol.360, pp. 2047-8, ISSN 0140-6736

Rintoul, NE. ; Sutton, LN. ; Hubbard, AM. ; Cohen, B.; Melchionni, J.; Pasquariello, PS. & Adzick, NS. (2002). A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. *Pediatrics*, Vol.109, pp. 409-413, ISSN 0031-4005

Rittler, M.; Lopez, CJ. & Castilla, EE. (2004). Sex ratio and associated risk factors for 50 congenital anomaly types: clues for causal heterogeneity. *Birth Defects Res A Clin Mol Teratol*, Vol.70, pp. 13-19, ISNN 15420752

Rowland, CA.; Correa, A.; Cragan, JD. & Alverson, CJ. (2006). Are encepaloceles neural tube defects? *Pediatrics*, Vol. 118, pp. 916-923, ISSN 0031-4005

Samaha, I. ; Rady, M. ; Nabhan, A. & Gadallah, M. (1995). The prevalence of congenital malformations at birth in Ain Shams University Maternity Hospital Cairo, Egypt, 1994. *J Egypt Public Health Assoc*, Vol.70, pp. 595-608, ISSN 0013-2446

Samson, GR. (2003). The incidence and demography of neural tube defects in Abu Dhabi, United Arab Emirates (1992-1999). *J Torp Pediatr*, Vol.49, pp. 256-257, ISSN 0142-6338

Selhub, J.; Jacques, PF.; Wilson, PWF.; Rush, D. & Rosenberg, IH. (1993). Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*, Vol.270, pp. 2693-2698. ISSN 0098-7484

Shields, DC.; Kirke, PN.; Mills, JL.; Ramsbottom, D.; Molloy, AM.; Burke, H.; Weir DG.; Scott, JM. & Whitehead, AS. (1999). The 'thermolabile' variant of methylenetetrahydrofolate reductase and neural tube defects: an evaluation of genetic risk and the relative importance of the genotypes of the embryo and the mother. *Am J Hum Genet*, Vol.64, pp. 1045-1055, ISSN 0002-9297

Smithells, RW.; Sheppard, S.; Schorah, CJ.; Seller, MJ.; Nevin, NC.; Harris, R.; Read, AP. & Fielding, DW. (1980). Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet*, Vol.1, pp. 339-40, ISSN 0140-6736

Soumaya, SG. ; Aida, M. ; Sami, M. ; Khaled, N.; Med Badis, C.; Sami, J.; Ezedine, S.; Zohra, M.; Issam, L.; Faouzia, Z.; Hedi, R.; Hela, C. & Naima, K. (2001). Encephalocele: 26 retrospective cases at the maternal and neonatal center of La Rabta, Tunis. *Tunis Med*, Vol.79, pp. 51-53, ISSN 0041-4131

Stevenson, RE. ; Allen, WP. ; Pai, GS.; Best, R.; Seaver, LH.; Dean, J. & Thompson, S. (2000). Decline in prevalence of neural tube defects in a high-risk region of the United States. *Pediatrics*, Vol.106, pp. 677-683, ISSN 0031-4005

The Centers for Disease Control and prevention (CDC). (1998). Preventing Neural Tube Birth Defects: A Prevention Model and Resource Guide. Atlanta, GA 30333.

Tuncbilek, E.; Boduroglo, K. & Alikasifoglu, M. (1999). Neural tube defects in Turkey: prevalence distribution and risk factors. *Turk J Pediatr*, Vol.41, pp. 299-305, ISNN 0041-4301

Van Allen, MI.; Fraser, FC. ; Dallaire, L.; Allason, J.; McLeod, DR.; Andermann, E. & Friedman, JM. (1993). Recommendations on the use of folic acid supplementation to prevent the recurrence of neural tube defects. Clinical Teratology Committee, Canadian College of MedicalGeneticists. *Can Med Assoc J*, Vol.149, pp. 1239-1243, ISSN 0820-3946

van der Put, NMJ.; Gabreëls, F.; Stevens, EMB.; Smeitink, JAM.; Trijbels, FJM.; Eskes, T.; van den Heuvel, LP. & Blom, HJ. (1998). A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural tube defects? *Am J Hum Genet,* 1998; Vol.62, pp. 1044-1051, ISSN 0002-9297

van der Put, NMJ.; Steegers-Theunissen, RPM.; Frosst, P.; Trijbels, FJM.; Eskes, TKAB.; van den Heuvel, LP.; Mariman, ECM.; den Heyer, M.; Rozen, R. & Blom, HJ. (1995). Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. *Lancet*, Vol.346, pp. 1071-1072. ISSN 0140-6736

van der Put, NMJ.; Thomas, CMG.; Eskes, TKA.; Trijbels, FJM.; Steegers-Teunissen, RPM.; Mariman, ECM.; de Graaf-Hess, A.; Smeitink, JAM. & Blom, HJ. (1997). Altered folate and vitamin B12 metabolism in families with spina bifida offspring. *Q J Med*, Vol.90, pp. 505-510, ISSN 1460-2725

Verrotti, A.; Tana, M.; Pelliccia, P.; Chiarelli, F. & Latini, G. (2006). Recent advances on neural tube defects with special reference to valproic acid. *Endocer Metab Immune Disord Drug Targets*, Vol.6, pp. 25-31, ISSN 1871-5303

Wasant, P. &, Sathienkijkanchai, A. (2005). Neural tube defects at Siriraj hospital, Bangkok, Thailand-10 years review (1990-1999). *J Med Assoc Tha*, Vol.88, pp. 92-99, ISSN 0125-2208

Williams, LJ. ; Rasmussen, SA. ; Flores, A.; Kirby, RS. & Edmonds, LD. (2005). Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. *Pediatrics*, Vol.116, pp. 580-6, ISSN 0031-4005

Williamson, RA.; Schauberger, CW.; Varner, MW.; & Aschenbrener, CA. (1984). Heterogeneity of prenatal onset hydrocephalus: Management and counseling implications. *Am J Med Genet*, Vol. 17, pp. 497-504, ISSN 0148-7299

Wilson, RD. & Van Allen, MI. (1993). Recommendations on the use of folic acid for the prevention of neural tube defects. *J Soc Obstet Gynecol*, Vol.15, pp. 41-44, ISSN 1488-2329

Windham, GC. & Edmands, LD. (1982). Current trends in the incidence of neural tube defects. *Pediatrics*, Vol.70, pp. 333-337, ISNN 0031-4005.

Xiao, KZ. ; Zhang, ZY. ; Su, YM. ; Liu, FQ. ; Yan, ZZ.; Jiang, ZQ.; Zhou, SF.; He, WG.; Wang, BY. & Jiang, HP. (1990). Central nervous system congenital malformations, especially neural tube defects in 29 provinces, metropolitan cities and autonomous regions of China: Chinese Birth Defects Monotoring Program. *Int J Epidemiol*, Vol.19, pp. 978-982, ISSN 0300-5771

Zaoui, S. & Biemont, C. (2002). Frequency of consanguineous unions in the Tlemcen area (West Algeria). *Santé*, Vol.12, pp. 289-295, ISSN 1157-5999

Zlotogora, J. (1997). Genetic disorders among Palestinian Arabs: 1. Effects of consanguinity. *Am J Med Genet*, Vol.68, pp. 472-475, ISSN 1532-4825
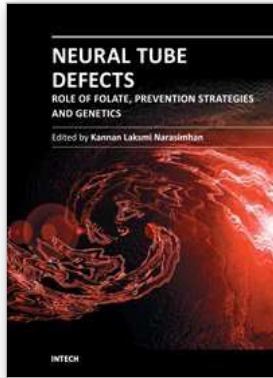
Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics

Edited by Dr. Kannan Laksmi Narasimhan

ISBN 978-953-51-0317-2

Hard cover, 200 pages

Publisher InTech

Published online 16, March, 2012

Published in print edition March, 2012

The book Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics has several eminent international authors and the book is a resource for anybody who is interested in this very important subject. The authors are distinguished and the chapters are a product of their extensive research.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Bakhouche Houcher, Samia Begag, Yonca Egin and Nejat Akar (2012). Neural Tube Defects in Algeria, Neural Tube Defects - Role of Folate, Prevention Strategies and Genetics, Dr. Kannan Laksmi Narasimhan (Ed.), ISBN: 978-953-51-0317-2, InTech, Available from: http://www.intechopen.com/books/neural-tube-defects-role-of-folate-prevention-strategies-and-genetics/neural-tube-defects-in-algeria-

INTECH
open science | open minds