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Neural Tube Defects in Algeria

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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).

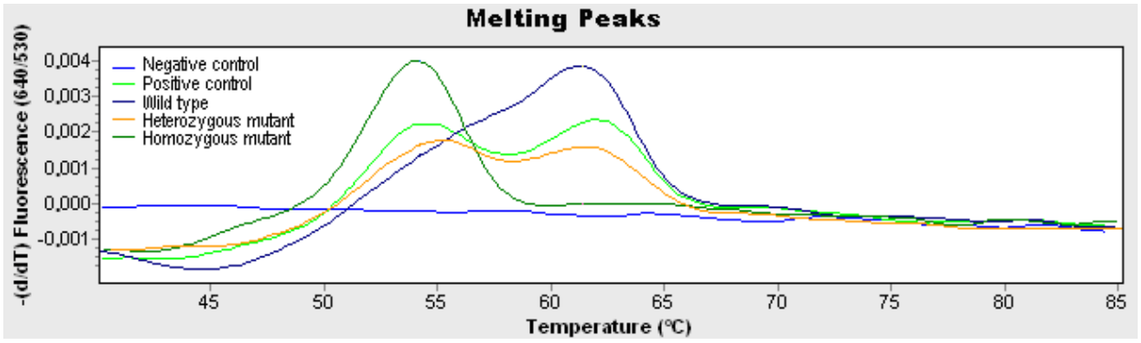

Fig. 1. Melting-curve analysis was performed analyze the MTHFR C677T polymorphism

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 No. (%)	Anencephaly No. (%)	Spina bifida +Anencephaly No. (%)	Encephalocele 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.

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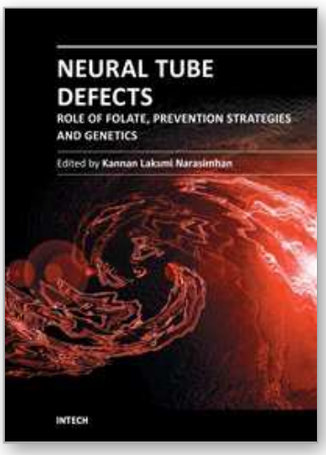

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