Neural Tube Defect, Folate-Sensitive

Alternative Names
NTD, Folate-Sensitive

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
601634

Mode of Inheritance
? Autosomal recessive

Gene Map Locus
1q43, 14q24, 5p15.3-p15.2

Description
The development of the neural tube in the mammalian embryo is a tightly regulated process controlled by multiple genes that can be modulated by environmental perturbations. Etiologic factors frequently associated with neural tube defects include chromosomal abnormalities, single gene defects, maternal diabetes, and anticonvulsant drugs, although it is generally agreed that most neural tube defects are multifactorial in origin. Recent studies have suggested that the risk of having a child with neural tube defect due to a gene and/or nutrient interaction is largely preventable by periconceptional supplements with folic acid.

The pathogenetic mechanisms underlying neural tube defect risk remain poorly understood. Whereas the vast majority of neural tube defects result from a primary failure of the neural tube to properly close. About 80% of embryos surviving up to nine weeks with neural tube defects have been reported to have concurrent chromosomal abnormalities. Interestingly, trisomy has been found to be the most common chromosomal anomaly associated with neural tube defects.

Molecular Genetics
The MTHFR 677 C-T polymorphism decreases enzyme activity and raises the dietary requirement for folic acid to maintain normal remethylation of homocysteine to methionine. Chronic elevation in intracellular homocysteine can lead to an increase in SAH and potent product inhibition of the DNA methyltransferase leading to DNA hypomethylation. DNA hypomethylation during embryogenesis has been proposed to negatively affect chromatin structure and critical regulatory genes required for normal development. There is also evidence that chronic folate/methyl deficiency can lead to chromosome instability, and aberrant chromosome segregation.

Epidemiology in the Arab World

Oman
Rajab et al. (1998) carried out a retrospective study to determine the incidence of neural tube defects (NTD) and congenital hydrocephalus (CH) in Oman. National data retrieved from hospital records revealed the incidence of NTD in Oman to be comparatively low (1.25 per 1000). There were no specific environmental factors associated with NTD and high environmental temperatures during the tropical desert summer (temperatures reach 48 degrees C) were excluded as a causative factor. In spina bifida families, later born children were more likely to be affected and there was also an association with increased maternal but not paternal age. Rajab et al. (1998) observed a much higher consanguinity rates in families with NTD and CH than in the general population.

Palestine
Dudin (1997) conducted a preliminary study to estimate the incidence of neural tube defect (NTD) among Palestinians living in East Jerusalem and the southern part of the West

Bank (600,000 inhabitants). Between 1 January 1986 and 31 December 1993, all NTD in fetuses weighing more than 500 g or of more than 22 weeks gestation, whether the product of abortion, therapeutic termination, stillborn or liveborn, were included. The study included 26,934 consecutive newborns. There were 148 cases of NTD, an incidence of 5.49 per 1000 births. The female to male ratio was 1.5:1. The incidences of spina bifida, encephalocele and anencephaly were 2.23, 0.44 and 2.41 per 1000, respectively. The incidence of NTD increased with maternal age.

In 1997, Zlotogora analyzed 2000 Palestinian Arabic families and found that in 98 families at least one individual had congenital hydrocephalus and/or open neural tube defect. In 76 of the families the neural tube defect and/or the hydrocephalus were non-syndromal. In 47 families at least one individual was affected with an open neural tube defect. Among individuals with open neural tube defects, there was a relatively large number with occipital cephalocele. Analysis of the associated malformations of the family data demonstrated that many cases with occipital cephalocele were affected with Meckel or Warburg syndrome.

In 2001, Al-Gazali et al. described a male child of a first-cousin couple of Palestinian origin who had Down syndrome and neural tube defect. The mother did not take periconceptional vitamins or folic acid supplements. The child also presented cervical meningomyelocele, agenesis of corpus callosum, hydrocephaly, cerebellar herniation into the foramen magnum, and shallow posterior cranial fossa. The had a five-fold increase in cystathionine level relative to normal children, consistent with over-expression of the cystathionine beta synthase gene present on chromosome 21.

Sudan

Nugud et al. (2003) conducted a restrospective study of 43 patients with neural tube fusion defects. Nugud et al. (2003) did not find significant difference in male and female ratio. Maternal diabetes was reported in 9% of cases. The sib recurrence rate was 7.0%. The pattern of defect showed, 4.6% spina bifida occulta, 90.8% cystica and the latter showed 11.6% meningoceles and 88.4% myelomeningocele, 4.6% encephalocele and no anencephaly. Associated anomalies included 34.9% club foot, 23.3% hydrocephalus, 2.3% facial clefts, and 2.3% polycystic kidneys. Approximately 83.7% of the patients were from Arab tribes and 16.3% from Negro tribes. Nugud et al. (2003) concluded that neural tube defects have a higher incidence during winter in Sudan and mostly in the first born child.

United Arab Emirates

Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth at Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 and January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with major malformation. Multifactorial disorders accounted for 26% of the cases. In their study, Al Talabani et al. (1998) observed 12 cases with neural tube defects from the United Arab Emirates. Recurrence was not reported in other members of the families. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the whole United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

Al-Gazali et al. (1999) prospectively studied 9,610 births in the three major hospitals in Al-Ain, United Arab Emirates (UAE) between October 1995 and January 1997. Of the 225 babies with congenital anomalies identified, 31 had central nervous system (CNS) abnormalities (3.2/1000). Syndromic abnormalities of the CNS were present in 13 cases (42%), chromosomal abnormalities in one case (3.2%) and the rest included: neural tube defect (NTD) in 11 cases (36%), holoprosencephaly in two cases (6.4%) and hydrocephalus in four cases (12.9%). Al-Gazali et al. (2001) noted that folic acid deficiency is endemic in the United Arab Emirates. [See also: Palestine > Al-Gazali et al., 2001].

References

Al Talabani J, Shubbar AI, Mustafa KE. Major congenital malformations in United Arab Emirates (UAE): need for genetic counselling. Ann Hum Genet. 1998; 62 (Pt 5):411-8.

Al-Gazali LI, Padmanabhan R, Melnyk S, Yi P, Pogribny IP, Pogribna M, Bakir M, Hamid ZA, Abdulrazzaq Y, Dawodu A, James SJ. Abnormal folate metabolism and genetic polymorphism of the folate pathway in a child with Down syndrome and neural tube defect. Am J Med Genet. 2001; 103(2):128-32.

Al-Gazali LI, Sztriha L, Dawodu A, Bakir M, Varghese M, Varady E, Scorer J, Abdulrazzaq YM, Bener A, Padmanabhan R. Pattern of central nervous system anomalies

in a population with a high rate of consanguineous marriages. Clin Genet. 1999; 55(2):95-102.
Dudin A. Neural tube defect among Palestinians: a hospital-based study. Ann Trop Paediatr. 1997; 17(3):217-22.
Nugud A, Arbab M, Osman TM. Pattern of neural tube fusion defects in Sudan. Saudi Med J. 2003; 24:S54.
Rajab A, Vaishnav A, Freeman NV, Patton MA. Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. J Trop Pediatr. 1998; 44(5):300-3.
Zlotogora J. Genetic disorders among Palestinian Arabs. 2. Hydrocephalus and neural tube defects. Am J Med Genet. 1997; 71(1):33-5.

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