IMPLICATION OF GENETIC FACTORS IN NEURAL TUBE DEFECTS ETIOLOGY

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Abstract. Neural tube defects are a group of developmental abnormalities that results from failure of fusion of the caudal neural tube, representing one of the most common group of malformations of human structure. The etiology is thought to be multifactorial in the vast majority of the cases, but other possible causes are heterogeneous and include chromosome abnormalities, single gene disorders and teratogenic exposures. However, the exact cause is not known in most cases and etiology remains rather complex and poorly understood. The aim of this study was to provide evidence for a genetic contribution to the etiology of neural tube defects. Multifactorial defects have a significant genetic component that interacts with specific environmental factors. Our study aimed to identify some of these risk factors, but it also established an association between the occurence of neural tube defects with spontaneous abortions, aswell as with other congenital defects, that may be considered markers of early prenatal damage. Concordance of these defects in families also sustained implication of genetic factors in their etiology.

Keywords: neural tube defects, spina bifida, genetic factors

INTRODUCTION

Neural tube defects such as anencephaly and spina bifida are among the most common severe congenital defects of the central nervous system. It is estimated that about 1/500 to 1/1000 pregnancies result in neural tube defects. The incidence varies with geographic areas and ethnic groups. These anomalies frequently occur together in families and are considered to have common pathogenesis.

During pregnancy, the human brain and spine begin their development as a flat plate of cells, which rolls into a tube, called the neural tube. Neural tube defects may be caused by a defect in closure of this tube, which is normally closed by 28 days. If all or part of the neural tube fails to close, leaving an opening, this may be left exposed (80 % of the time), or covered with bone or skin, defect called spina bifida occulta (20 % of the time). Anencephaly and spina bifida are the most common, while encephaloceles, where there is a protrusion of the brain or its coverings through the skull, are much rarer. Anencephaly occurs when the neural tube fails to close at the base of the skull, whereas spina bifida occurs when the neural tube fails to close in an area along the spine. Cases with anencephaly are stillborn or usually live for only a few days after delivery, whereas those born with spina bifida may have minimal or temporary problems, or may have permanent, often serious physical problems, such as paralysis, lack of bowel and bladder control, club feet, hydrocephaly and mental retardation. In most cases, one or more surgeries after birth may be necessary [9].

Spina bifida is characterized by a failure of fusion of the arches of the vertebrae, typically in lumbar region, but also possible in other regions. There are varying degrees of severity, ranging from spina bifida occulta, in which the defect is in the bony arch only, to spina bifida aperta, often associated with meningocele or meningomyelocele. The incidence of neural tube defects seems a little higher in females than in males. Their frequency also appears to vary with social factors and season of birth. It has been believed that nutritional factors may account for at least part of the complex etiology [1, 5]. Specific causes are identified in less than 10% of affected subjects, such as amniotic bands, some single - gene defects with pleiotropic expression, chromosome abnormalities and teratogenic factors [20, 21]. A specific mutation known as C677T polymorphism was noticed to be more common in parents of children affected with neural tube defects. Low erythrocyte folate during the first trimester of pregnancy also seems to be associated with an increased risk.

Most neural tube defects are presumed to have multifactorial inheritance. Human development depends on genetic and environmental factors. Multifactorial inheritance, referring to the additive effects of many genetic and environmental factors, is responsible for several of developmental disorders resulting in congenital malformations [10]. In this case disorders tend to run in families, but their pattern of inheritance is not as predictable as with single gene ones. Empiric risks are used to predict the recurrence of neural tube defects of multifactorial etiology. This risk is based on epidemiologic and population studies and on mathematical models [22]. Neural tube defects are considered complex disorders because they are caused by a combination of multiple genes and environmental factors [4].

Neural tube defects occur in couples without a prior family history of these defects in over 90 % of cases. Once a child has been born with a neural tube defect in the family, the risk of having another affected child is increased to 3 to 5%. It is important to understand that the type of neural tube defect can differ the second time.

Microcephaly is defined as a neurodevelopmental disorder, clinically and genetically heterogeneous, which may be caused by genetic and environmental causes. Genetic factors have effects during the critical period of brain development. In some of the genetic conditions microcephaly is associated with an abnormal development of other parts of the body such as the limbs, the heart, or the eyes. The recurrence risk depends on the underlying cause. All patterns of single-gene inheritance for isolated microcephaly have been described [17].

The aim of the present study was to determine some etiologic aspects of neural tube defects, the extent of genetic factors contribution for neurodevelopmental conditions, but also implication of environmental agents in their causality. On the other hand epidemiological information regarding these types of congenital defects were also obtained, data that are useful for their diagnosis, prevention, treatment options and in health services planning.

MATERIALS AND METHODS

The study lot was formed by 13 subjects with neural tube defects, admitted in the Medical Rehabilitation Clinical Hospital Baile-Felix between September 2007-September 2009. Anomalies were represented by spina bifida, but additional 9 cases with microcephaly were also included. A complete family history was taken for each case in order to establish as accurate as posssible the etiology of the defect. For each subject elements that brought information about the case and family were gathered. Thus, the following data were registrated: mother′s age, rank of pregnancy, data about previous pregnancies, spontaneous abortions, evolution of the pregnancy, treatments or other possible teratogens during pregnancy, season of conception, infant′s height and weight at birth.

RESULTS

Total number of cases with spina bifida was 13, grouped as follows:

- 9 (69.23%) cases with meningomyelocele
- 1 (7.69%) case with meningocele
- 3 (23.03%) cases with spina bifida occulta

Study of variation of the incidence according to the sex of the subject revealed a slight increase of the incidence of spina bifida in males, sex ratio being F/M=0.857/1. As for microcephaly sex ratio was F/M=1.25/1.

The most common location of spina bifida was in the lumbar region, 4 cases (30.76%). 3 cases (23.07%) had the anomaly located in the thoraco-lumbar region. 2 cases (15.38%) were affected in the thoracic and lombo-sacral region, respectively. Other locations, cervical and sacral, were seen each in 1 subject (7.69%).

Regarding location of spina bifida according to the sex of the subject an almost uniform distribution was noticed for male sex, as the anomaly occured in each of the possible regions, but for females the lumbar area was the most frequent location (Fig. 1).

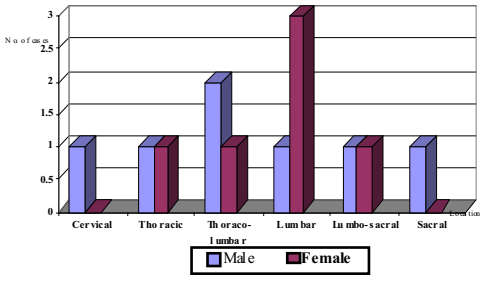

Figure 1. Location of spina bifida cases according to the sex of the subjects.

Considering other congenital anomalies associated with spina bifida it was noticed that the most frequently noticed defects were hydrocephaly and limb anomalies. 5 (38.4%) cases had hydrocephaly, 6 (46.15%) cases had limb deformities such as talus valgus, varus equin and 1 (7.69%) case had polydactyly. As for microcephaly the most frequently associated defects were congenital heart and lung defects, but within a plurimalformative syndrome hydrocephaly and limb defects were also present. 2 cases had eye anomalies: anophtalmy and hypertelorism, respectivelly (Fig. 2).

Regarding the number of births with affected subjects according to the season of conception, a maximum was noticed in August and October, higher values occuring during summer-autumn, compared to the rest of the year (Fig. 3).

In order to determine the extent of genetic factors implications, families with more than one affected case were studied. Thus, in one family 2 cases with spina bifida were found, known the fact that if there is already one affected case, the risk for another one is higher. Another family with 2 cases with microcephaly was also registrated. Concordance of these defects in families reveals implication of genetic factors in their etiology. We also tried to identify risk factors during pregnancy that might have had a teratogenic effect, as well as the presence of other affected cases in the fa-

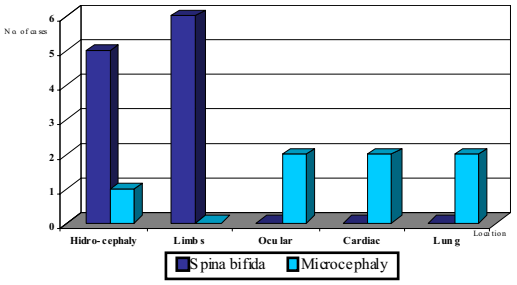

Figure 2. Association between spina bifida and microcephaly with other congenital defects.

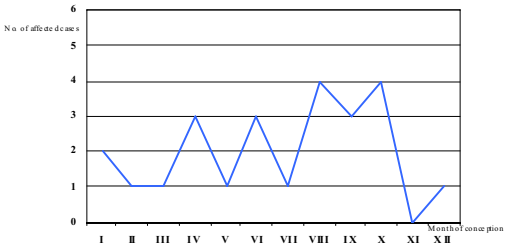

Figure 3. Number of births with spina bifida according to the month of conception.

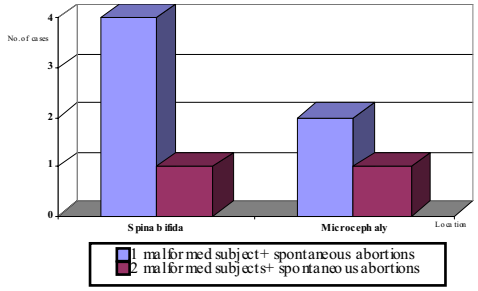

Figure 4. Association between spina bifida and microcephaly with spontaneous abortions.

milies, not only with neural tube defects or microcephaly, spontaneous abortions in the medical records, informations usefull to conclude that genetic factors were involved.

Obtained data revealed that from 13 cases with spina bifida, for 5 (38.4%) cases a history of spontaneous abortions was noticed in the family, as regarding microcephaly, from 9 families, 3 (33.3%) had such events in their history (Fig. 4).

DISCUSSIONS

Neural tube defects including spina bifida and anencephaly, represent severe congenital anomalies that result from failure of neural tube to close during early development. It is estimated that more than one third of the pregnancies with affected fetuses are spontaneously lost or electively terminated. It is estimated that 95% of cases with a neural tube defect are born to couples with no family history of these defects. Their etiology is quite complex involving environmental and genetic factors and their underlying molecular and cellular pathogenic mechanisms remain poorly understood. Based on epidemiological and clinical data obtained over the last decades, it results that these multifactorial defects have a significant genetic component to their etiology that interacts with specific environmental factors. Several lines of evidence suggest a genetic component most notably the increased rate of recurrence in siblings and the increased risk of defects in the offspring of a person with a neural tube defect. The recurrence risk for this type of inheritance is estimated at 2-3% for siblings of an affected case and 3-4% for offsprings of an affected individual. Spina bifida and anencephaly are closely related both genetically and in their pathogenesis, thus the recurrence risk is equally distributed for both regardless of which condition the index case had. Rarely, neural tube defects can occur as parts of a genetic syndrome, or may occur due to other causes such as nutritional deficiencies in particular folic acid deficiency, certain medication taken during pregnancy including antiepileptic drugs, maternal diabetes or obesity leading to different recurrence risks [2, 7]. Other potential risk factors have been suggested on the basis of epidemiological studies and include maternal diabetes mellitus, influenza A, hyperthermia, alcohol, or organic solvents.

Racial, geographic and seasonal variations seem to affect the incidence of these defects. Our observations are concordant with data from literature. Recent *in vitro* and *in vivo* studies have highlighted the molecular mechanisms of neurulation in vertebrates but the morphologic development of human neural tube is yet poorly understood. Animal studies have recently demonstrated an essential role for the planar cell polarity pathway in mediating a morphogenetic process called convergent extension during neural tube formation [14]. Alterations in members of this pathway lead to neural tube defects in vertebrate models, representing candidates for human neural tube defects. Numerous studies have been conducted to elucidate the genetic basis of normal human neurulation [23]. TEAD2, one of the first transcription factors expressed at the beginning of mammalian development, seems to be required during neural development [13]. Essential signaling pathways of the development of the central nervous system include the planar cell polarity pathway, which is important for initiation of neural tube closure, as well as the sonic hedgehog pathway, which regulates the neural plate bending [12]. To date, there is evidence that closure of the mammalian neural tube initiates and fuses intermittently at four discrete locations. Disruption of this process at any of these four sites may lead to neural tube defects possibly arising through closure site-specific genetic mechanisms [8].

The most important environmental risk factor for neural tube defect is insufficient folate consumption by the mother around the time of conception [3]. Genetic studies have focused mainly on folate-related genes based on the finding that perinatal folic acid supplementation reduces the risk of neural tube defects by 60-70%, but it does not entirely eliminate the risk suggesting underlying genetic factors, which are also sustained by studies of twins with neural tube defects, which have shown that both identical twins have the defects more frequently than both fraternal twins [6]. A few variants in these genes have been found to be significantly associated with an increased risk. Candidate genes involved in neural tube closure include genes of the folate metabolic pathway, as well as those involved in folate transport [15, 16]. Previous pregnancy wastage, parity, and fetal birth weight as well as certain parental occupations have also been implicated as risk factors [18, 19]. Genetic counseling is recommended to discuss the risk of recurrence in a future pregnancy [11].

Spina bifida may cause disabilities. Associated complications depend on the level and severity of the lesion [9]. Usually complications occur in spina bifida aperta, but they can occur in spina bifida occulta aswell. Cases with neural tube defects demand a long treatment and constant care of a specialist team which consists of: a pediatrician, pediatric surgeon, neurologist, nephrologist, specialist in rehabilitation and psychologist. Non-surgical management of spina bifida may include the following:

- Rehabilitation
- Positioning aids
- Braces and splints
- Medication

Kinetic rehabilitation program may include:

- McKenzie-based treatment for neck and back pain
- Lumbar stabilization/core strengthening
- Stretching and flexibility exercises
- Progressive lower extremity strengthening exercises
- Manual therapy and mobilization techniques
- Muscle energy techniques
- Therapeutic modalities
- Pilates exercises
- Postural exercises and training
- Body mechanics and functional training

In the treatment of the cases with spina bifida, rehabilitating treatment is the basic and main one, which is started in the first days of life.

As neural tube defects raise complex medical, social but also financiar problems it is necessary that a pluridisciplinary team should be involved in their management. The final goal is to prevent the occurence of these severe defects, avoiding risk factors that may directly interfere normal morphogenesis, or may somehow transform genetic predisposition into a congenital defect.

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