CURRENT OPINION ON ETIOLOGY OF CLUBFOOT

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S u m m a r y. Congenital talipes equinovarus (clubfoot) is one of the most common congenital defects of the musculoskeletal system. Because of the defect high prevalence and the disability it may cause, it comprises a substantial social problem. The recognition of the predisposing genetic and environmental factors is the key to prevention and adequate treatment. The aim of this review is to present current opinion on the etiology of clubfoot including genetic and environmental factors.
K e y w o r d s: congenital talipes equinovarus, clubfoot, etiology.

INTRODUCTION

Congenital talipes equinovarus (clubfoot) is one of the most common birth defect. Clubfoot presents itself in two forms: associated with other defects such as myelodysplasia, arthrogryposis or amniotic band syndrome, and idiopathic. The clinical presentation of clubfoot comprise of hindfoot equinus, midfoot cavus, hindfoot varus and forefooot adductus. Prevalence depends on the ethnic group and varies from 0,39/1000 for Chinese population to 6,8/1000 in Hawaiians and Maoris with the average of 1/1000 of live births. Boys are affected twice as often as girls, half of the cases is bilateral, when unilateral more often affects the right limb [10, 11].

ETIOLOGY

The first description of clubfoot comes from V century b. c. Hippocrates believed intrauterine pressure to be the cause of clubfoot. This theory returned many times but no conclusive data supports it [3]. Clubfoot develops at such an early stage of intrauterine growth, that it is impossible for the uterus to 'mold' the embryo.

GENETIC FACTORS

Contemporary research shows that clubfoot pathogenesis in the Caucasian population is multifactorial with some polygenic inheritance. Also, the polygenic threshold model with sex dimorphism, called the Carter effect, has been used to describe the inheritance pattern in clubfoot. Earlier this phenomenon was described for pylorostenosis, sclerosis multiplex and familial malignant melanoma. In this model, females require the larger number of susceptibility genes to demonstrate the defect in phenotype. Because of that, clubfoot in females is more severe and more bilateral than in males, have a worse prognosis on treatment and females have a higher rate of transmission to their offspring [9].

Clubfoot genetic etiology comes from the fact that the defect occurs in 33% of both monozygotic twins and for dizygotic ones the prevalence is similar to normal siblings [12]. Also, a family occurrence of about 25% [10] and the prevalence change depending on the population is another proof of clubfoot genetic etiology.

The model of clubfoot inheritance varies among different populations. The studies of New Zealand Maori and Polynesian [4] show that the best genetic clubfoot model among these populations is a single dominant gene with a penetrance of 33%. Another study of a Polynesian family with

a multigenerational occurrence of clubfoot allows to identify a missense mutation of *PITX1* gene [7]. *PITX1* haploinsufficiency is associated with clubfoot in humans and causes a clubfoot like phenotype in genetically modified mice [2]. The same authors in another study recognize *TBX4* gene also associated with clubfoot and other defects of the musculoskeletal system [1]. Both *PITX1* and *TBX4* genes are only expressed in the lower limb which correlates with the phenotype caused by their mutations [5].

Other important factors include apoptotic genes. The correct function of apoptotic genes involved in the cell death signaling cascade are critical for embryogenesis. Any alteration in this process lead to structural defects. A study of a single nucleotide polymorphisms in apoptotic genes: *CASP3, CASP8, CASP9, CASP10, CFLAR, BCL-2* in patients with familial clubfoot showed their association with clubfoot etiology [6].

EXTRINSIC FACTORS

Significant environmental factors include: maternal smoking, maternal diabetes and folic acid supplementation. Maternal smoking shows a strong correlation with higher clubfoot prevalence in comparison to the control group [3,11]. Homein et al. [8] showed a 20 fold increase in the clubfoot occurrence risk in case of maternal smoking and a family history of clubfoot. Most studies showed also a dose dependent effect [3].

Maternal diabetes is significantly associated with clubfoot. The clubfoot risk is increased more than twofold among women with pregestational diabetes, whereas the risk increase associated with gestational diabetes is modest [11].

Folic acid is critical for the DNA synthesis. Folic acid deficiency hinders DNA synthesis and cell division. Adequate folic acid intake helps prevent neural tube defects. The supplementation with folic acid 3 months before pregnancy and during the first trimester is associated with a decrease in the clubfoot risk [3].

CONCLUSIONS

Clubfoot etiology is complex and both environmental and genetic factors play a role. The effect of genes is modified by many factors such as interactions between genes and environmental factors. Further studies and the understanding of genetics and pathogenesis of idiopathic congenital talipes equinovarus will allow genetic counseling and the new clubfoot classification which will better correlate with the functional outcome of the treatment. New environmental risk factors identification improves pophylaxis guidelines.

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